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Cardiomyopathy

Clinical Implications of Midventricular Obstruction in Patients With Hypertrophic Cardiomyopathy

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Objectives	We investigated the prevalence, clinical characteristics, and prognosis of hypertrophic cardiomyopathy (HCM) patients with midventricular obstruction (MVO).
Background	Previous descriptions of patients with MVO have been confined to case reports or small patient series, and this subgroup of HCM patients has therefore remained underrecognized.
Methods	The study population included 490 HCM patients. Left ventricular MVO was diagnosed when the peak midcavitary gradient was estimated to be $\geq$30 mm Hg.
Results	MVO was identified in 46 patients (9.4%). Patients with MVO were more likely to be symptomatic than those without. MVO was found to be an independent determinant of HCM-related death in multivariate models (hazard ratio [HR]: 2.23, p = 0.016), and this trend was especially pronounced for the combined endpoint of sudden death and potentially lethal arrhythmic events (HR: 3.19, p < 0.001). Apical aneurysm formation was identified in 28.3% of patients with MVO and strongly predicted HCM-related death (HR: 3.47, p = 0.008) and the combined endpoint of sudden death and potentially lethal arrhythmic events (HR: 5.08, p < 0.001). In addition, MVO without apical aneurysm was also identified as an independent determinant of the combined endpoint of sudden death and potentially lethal arrhythmic events (HR: 2.43, p = 0.045).
Conclusions	This analysis identified MVO as an independent predictor of adverse outcomes, especially the combined endpoint of sudden death and potentially lethal arrhythmic events. Our results suggest that longer periods of exposure to MVO might lead to unfavorable consequences. They also support the principle that the presence of MVO in patients with HCM has important pathophysiological implications. (J Am Coll Cardiol 2011;57:2346–55) © 2011 by the American College of Cardiology Foundation

Hypertrophic cardiomyopathy (HCM) is a genetic cardiac disease characterized by marked variability in morphological expression and natural history (1). Left ventricular intracavitary obstruction is an important pathophysiological component of HCM and classically occurs at the subaortic level, mainly due to systolic anterior motion (SAM) of the anterior mitral valve leaflet (1). This subaortic obstruction, called left ventricular outflow tract obstruction (OTO), occurs at rest in approximately 25% of patients with HCM and is an independent predictor of adverse clinical consequences (2,3). In a minority of HCM patients, however, the impedance to flow occurs at the midcavitary level, unrelated to SAM, and is predominantly caused by marked septal hypertrophy coming in contact with a hypercontractile left

ventricular free wall, often with the interposition of the hypertrophied papillary muscle (4). Previous descriptions of these patients with midventricular obstruction (MVO) have been confined to case reports or small patient series because of the relative rarity and unique pathophysiology of the condition (5–13). Consequently, this subgroup of patients with HCM has remained underappreciated, and the clinical profiles of patients with MVO are largely undefined. This study was therefore undertaken to investigate the prevalence, clinical characteristics, and long-term prognosis of HCM patients with MVO.

Methods

Patients. The study population included 490 patients with clinically diagnosed HCM who were enrolled and evaluated from 1980 to 2005 at Tokyo Women's Medical University Hospital, Tokyo, Japan. The initial evaluation was the first clinical assessment during which an echocardiogram diagnostic of HCM was obtained, and the most recent evaluation was

performed in the clinic or by telephone interview. The study was performed according to the principles of the Declaration of Helsinki, and the study protocol was approved by the institutional ethics committee.

HCM. The diagnosis of HCM was based on the identification by 2-dimensional echocardiography 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).

OTO and MVO. Left ventricular OTO, caused by SAM of the anterior mitral valve leaflet, was considered to be present when the estimated peak instantaneous gradient was ≥30 mm Hg (3,14). Left ventricular MVO was diagnosed when both of the following criteria were satisfied: 1) the peak instantaneous midventricular gradient was estimated to be ≥30 mm Hg; and 2) midventricular obliteration was caused by marked septal hypertrophy resulting in contact with a hypercontractile left ventricular free wall rather than by SAM of the anterior mitral valve leaflet (6). Patients with both OTO (SAM) and MVO were excluded from the MVO group and included in the OTO group (6). This accounted for 6 of the 110 OTO patients (5.5%) in the current study.

Apical hypertrophy and aneurysm. The diagnostic criteria for apical hypertrophy included asymmetrical left ventricular hypertrophy, confined predominantly to the left ventricular apex, with an apical wall thickness ≥15 mm (15). A left ventricular apical aneurysm was defined as a discrete, thin-walled dyskinetic or akinetic segment of the most distal portion of the chamber with a relatively wide communication to the left ventricular cavity (16).

Arrhythmias. Documentation of atrial fibrillation was based on electrocardiographic recordings obtained either after acute onset of symptoms or fortuitously during routine medical examinations in asymptomatic patients. Ambulatory electrocardiograms covering at least a 24-h period were reviewed in all patients for the occurrence of nonsustained ventricular tachycardia, defined as a minimum of 3 consecutive ventricular beats with a rate of ≥120 beats/min (1).

Mode of death. Three modes of HCM-related death were defined for the purposes of survival analysis (1): 1) a combined endpoint of sudden death and potentially lethal arrhythmic events, in which unexpected death occurred in the absence of or <1 h from symptom onset in patients who had previously experienced a relatively stable or uneventful course, including resuscitated cardiac arrest and appropriate implantable defibrillator interventions; 2) heart failure–related death in the context of progressive cardiac decompensation ≥1 year before death, particularly if complicated by pulmonary edema or evolution to end-stage phase; and 3) stroke-related death, which occurred in patients who died as a result of ischemic stroke.

Echocardiography. Echocardiographic studies were performed using commercially available ultrasound equipment. Complete M-mode, 2-dimensional, and Doppler studies were performed with the patient in the left lateral decubitus

or supine position, using standard parasternal, apical, and subcostal approaches. Color Doppler imaging and pulse-wave Doppler echocardiography were used to localize the site of obstruction. Peak left ventricular intracavitary gradient was quantified using continuous-wave Doppler echocardiography under resting conditions. MVO was defined by systolic apposition of the mid-left ventricular walls, and often the papillary muscles, with abnormally high velocities persisting through late systole and often with early diastolic paradoxical jet flow (13). Contrast-enhanced echocardiography was performed by manual intravenous injection of 300 mg/ml galactose-palmitic acid (Levovist, Schering, Berlin, Germany) at a rate of 5 ml/5 s.

Abbreviations and Acronyms
CI = confidence interval
CMR = cardiovascular magnetic resonance
HCM = hypertrophic cardiomyopathy
HR = hazard ratio
MVO = midventricular obstruction
OTO = outflow tract obstruction
SAM = systolic anterior motion

Cardiovascular magnetic resonance (CMR) imaging. Studies were performed using a Magnetom Vision 1.5-T whole-body imaging system (Siemens Medical Systems, Erlangen, Germany [used from 2001 to July 2003]), or a Gyroscan Intera (Philips Medical Systems, Best, the Netherlands [used from July 2003 to 2005]). Breath-hold electrocardiography-gated cine steady-state free precession images were acquired in 7 to 10 short-axis slices and standard 2- and 4-chamber long-axis orientations. A delayed enhancement protocol was used 10 min after intravenous administration of 0.10 to 0.15 mmol/kg gadolinium-diethylenetriaminepentaacetic acid (Magnevist, Schering) with a breath-held segmented inversion-recovery sequence (inversion time, 230 to 300 ms, adjusted by a look-locker sequence) acquired in the same views as the cine images.

Statistical analysis. Analyses were performed using SAS system software, version 9.1 (SAS Institute, Cary, North Carolina). Data were presented as mean ± SD and frequencies. Student t tests were used to compare values between the 2 groups for continuous variables, and Mann-Whitney U tests were used for ordinal variables. Normality of distribution was assessed using the Kolmogorov-Smirnov test, and equality of variances was checked using the F statistic. A chi-square or Fisher exact test (when an expected value was <5) was used to compare nominally scaled variables. Event-free curves were estimated using the Kaplan-Meier method, and differences between curves were assessed by log-rank tests. Univariate and multivariate Cox proportional hazards models were applied to evaluate the influence of MVO and MVO with or without apical aneurysm on HCM-related death and the combined endpoint of sudden death and potentially lethal arrhythmic events. The proportional hazards assumption was confirmed by the log (−log survival function). The influences of profile, interaction, and collinearity in the models were examined using

regression diagnostic analysis. A 2-tailed p value <0.05 was considered to indicate a statistically significant difference.

Results

Prevalence and baseline characteristics. MVO was identified in 46 of 490 HCM patients (9.4%). The baseline demographic and clinical characteristics of the HCM patients with and without MVO are shown in Table 1. The mean age at diagnosis of the 46 patients with MVO was 53.2 ± 14.7 years (range 19 to 77 years). The New York Heart Association functional class at diagnosis in patients with MVO was significantly higher than that in those without MVO. However, there were no statistically significant differences with respect to sex, age, family history of sudden death, maximal left ventricular wall thickness, or arrhythmias between patients with and without MVO.

Comparison with OTO and treatments. OTO was identified in 110 of 490 HCM patients (22.4%). The demographic, clinical, and therapeutic characteristics of the 46 patients with MVO and the 110 patients with OTO are shown in Table 2. There was a higher proportion of male patients with MVO than with OTO, and patients with MVO had a lower left ventricular intracavitary gradient at diagnosis. Of the 46 patients with MVO, 43 (93.5%) were treated with negative inotropic agents, such as beta-blockers, calcium-channel blockers, and/or class I antiar-rhythmic drugs (mainly disopyramide). Three patients (6.5%) underwent dual-chamber pacing therapy, and only 1 patient (2.2%) underwent surgery to reduce the gradient caused by MVO.

Outcomes. Six of the 46 patients with MVO (13.0%) experienced episodes of progressive heart failure with an increase to ≥3 New York Heart Association functional class, and 5 patients (10.9%) had nonfatal thromboembolic strokes over the mean follow-up period of 10.4 ± 8.2 years. Eleven patients (23.9%) experienced HCM-related death including 2 patients with sudden death, 7 patients with successfully resuscitated cardiac arrest (with documented ventricular fibrillation [n = 5] and with documented ventricular tachycardia with pulseless collapse [n = 2]), and 2 patients with appropriate implantable defibrillator interventions. In univariate analysis, patients with MVO had a significantly greater likelihood of HCM-related death than patients without MVO (log-rank p = 0.017) (Fig. 1A). The probability of the combined endpoint of sudden death and potentially lethal arrhythmic events among patients with MVO was also significantly higher than that among patients without MVO (log-rank p < 0.001) (Fig. 1B). The frequency of HCM-related death in patients with MVO was similar to that in patients with OTO (log-rank p = 0.451) (Fig. 2A). Conversely, the probability of the combined endpoint of sudden death and potentially lethal arrhythmic events among patients with MVO was significantly higher than that among patients with OTO (log-rank p = 0.038) (Fig. 2B). In multivariate modeling, entering MVO and established major primary prevention risk factors for sudden death (family history of sudden death, maximum left ventricular wall thickness ≥30 mm, nonsustained ventricular tachycardia, and unexplained syncope) (1,17), MVO was identified as an independent determinant of outcome, including the risk of HCM-related death (adjusted hazard ratio [HR]: 2.23, 95% confidence interval [CI]: 1.16 to 4.29; p = 0.016) and the combined endpoint of sudden death and potentially lethal arrhythmic events (adjusted HR: 3.19, 95% CI: 1.62 to 6.29; p < 0.001) (Table 3). Exercise tests were not performed in all HCM patients, and abnormal exercise blood pressure was therefore excluded from the analysis. The sensitivities of MVO for HCM-

Table 1 Baseline Characteristics of HCM Patients With and Without MVO			
	Patients With MVO (n = 46)	Patients Without MVO (n = 444)	p Value
Male	28 (60.9)	288 (64.9)	0.590
Age at diagnosis, yrs	53.2 ± 14.7	50.4 ± 14.9	0.232
Family history of sudden death	6 (13.0)	55 (12.4)	0.898
Maximal left ventricular wall thickness, mm	19.1 ± 4.3	19.7 ± 4.2	0.345
Apical aneurysm formation	13 (28.3)	8 (1.8)	<0.001
Nonsustained ventricular tachycardia	14 (30.4)	182 (41.0)	0.164
Atrial fibrillation	11 (23.9)	140 (31.5)	0.287
Unexplained syncope	12 (26.1)	80 (18.0)	0.182
NYHA functional class at diagnosis			0.004
I	13 (28.3)	247 (55.6)	
II	31 (67.4)	159 (35.8)	
III	2 (4.3)	35 (7.9)	
IV	0 (0.0)	3 (0.7)	
Progressive heart failure	6 (13.0)	53 (11.9)	0.826
Stroke	5 (10.9)	56 (12.6)	0.733
Follow-up duration, yrs	10.4 ± 8.2	11.7 ± 7.3	0.266

Values are n (%) or mean ± SD.
HCM = hypertrophic cardiomyopathy; MVO = midventricular obstruction; NYHA = New York Heart Association.

Table 2	Demographic, Clinical, and Therapeutic Characteristics of HCM Patients With MVO and With OTO		
	Patients With MVO (n = 46)	Patients With OTO (n = 110)	p Value
Male	28 (60.9)	48 (43.6)	0.050
Age at diagnosis, yrs	53.2 ± 14.7	55.1 ± 15.7	0.483
Family history of sudden death	6 (13.0)	11 (10.0)	0.578
Maximum left ventricular wall thickness, mm	19.1 ± 4.3	20.0 ± 4.9	0.239
Apical aneurysm formation	13 (28.3)	2 (1.8)	<0.001
Nonsustained ventricular tachycardia	14 (30.4)	36 (32.7)	0.780
Atrial fibrillation	11 (23.9)	36 (32.7)	0.274
Unexplained syncope	12 (26.1)	22 (20.0)	0.401
NYHA functional class at diagnosis			0.927
I	13 (28.3)	39 (35.5)	
II	31 (67.4)	57 (51.8)	
III	2 (4.3)	13 (11.8)	
IV	0 (0.0)	1 (0.9)	
Progressive heart failure	6 (13.0)	14 (12.7)	0.957
Stroke	5 (10.9)	13 (11.8)	0.866
Pressure gradient at diagnosis, mm Hg	45.9 ± 14.7	81.0 ± 30.1	<0.001
Treatments			
Beta-blockers	35 (76.1)	92 (83.6)	0.269
Calcium-channel blockers	14 (30.4)	26 (23.6)	0.375
Class I antiarrhythmic drugs	16 (34.8)	69 (62.7)	0.001
All interventions combined	4 (8.7)	36 (32.7)	0.002
Warfarin	13 (28.3)	35 (31.8)	0.661
Follow-up duration, yrs	10.4 ± 8.2	10.0 ± 6.7	0.761

Values are n (%) or mean ± SD.
OTO = outflow tract obstruction; other abbreviations as in Table 1.

related death/combined endpoint of sudden death and potentially lethal arrhythmic events were 17.2%/22.9%, respectively, and the corresponding specificities were 91.8%/92.1%, respectively.

Apical hypertrophy and apical aneurysm formation. Left ventricular apical hypertrophy was identified in 16 of the 46 patients with MVO (34.8%). All the 16 patients exhibited mid-left ventricular hypertrophy, and none had hypertrophy
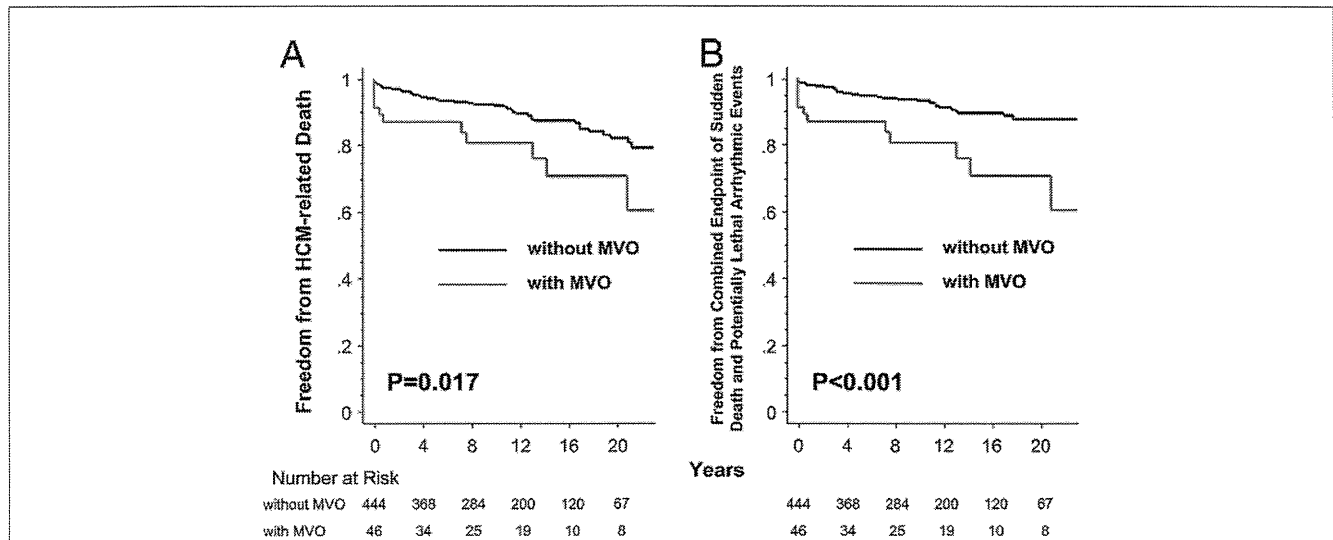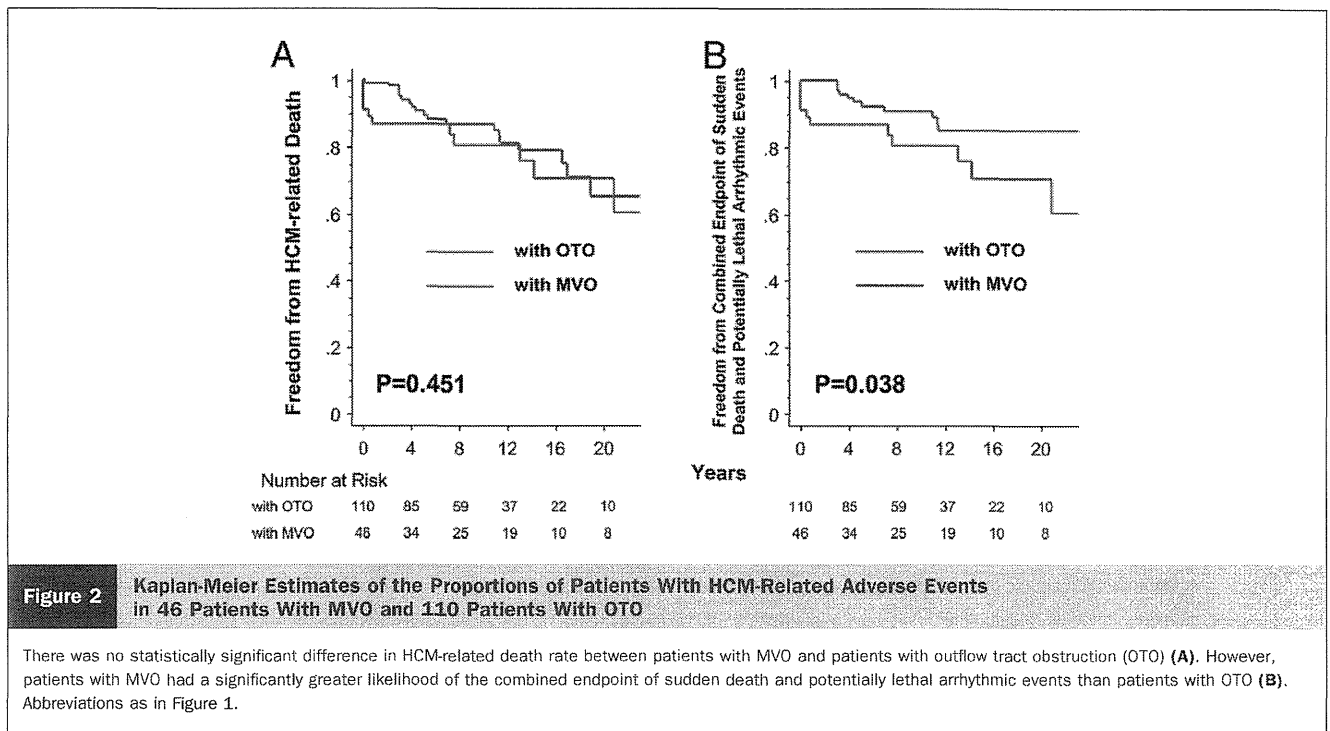

Figure 1	Kaplan-Meier Estimates of the Proportions of Patients With HCM-Related Adverse Events in 46 Patients With MVO and 444 Patients Without MVO

Patients with midventricular obstruction (MVO) had a significantly greater likelihood of hypertrophic cardiomyopathy (HCM)-related death **(A)** and the combined endpoint of sudden death and potentially lethal arrhythmic events **(B)** than patients without MVO.

Figure 2   Kaplan-Meier Estimates of the Proportions of Patients With HCM-Related Adverse Events in 46 Patients With MVO and 110 Patients With OTO

There was no statistically significant difference in HCM-related death rate between patients with MVO and patients with outflow tract obstruction (OTO) **(A)**. However, patients with MVO had a significantly greater likelihood of the combined endpoint of sudden death and potentially lethal arrhythmic events than patients with OTO **(B)**. Abbreviations as in Figure 1.

confined only to the left ventricular apex below the papillary muscle level. Left ventricular apical aneurysm was identified in 13 of the 46 patients with MVO (28.3%). Coronary artery disease was excluded as a cause of apical aneurysm formation by the absence of significant coronary arterial narrowing (>50% stenosis) in the left anterior descending artery using conventional coronary angiography (n = 10) and no history of chest pain, coronary risk factors, or acute coronary syndrome (n = 3, all younger than 60 years of age). An apical aneurysm was confirmed by CMR in 8 of the 13 patients. All the 8 patients exhibited late gadolinium enhancement in the apical aneurysmal wall itself, with extension into the hypertrophic region of the left ventricle. An apical aneurysm was confirmed by contrast-enhanced echocardiography in the remaining 5 patients who did not undergo CMR. Development of an apical aneurysm from MVO was observed in 6 of 13 aneurysm patients during the follow-up period (Figs. 3 and 4). In the remaining 7 patients, an apical aneurysm was observed at the initial evaluation. In 2 of 6 patients in whom an apical aneurysm developed from MVO, CMR was performed both before and after aneurysm formation, and these 2 patients already exhibited late gadolinium enhancement in the apex before detection of the apical aneurysm formation (Fig. 3C). The baseline characteristics of the HCM patients with MVO, according to the presence or absence of an apical aneurysm, are shown in Table 4. The frequency of nonsustained ventricular tachycardia in patients with an aneurysm was significantly higher than in those without an aneurysm. In contrast to the situation in patients with MVO, only 2 of the 110 patients with OTO (1.8%), and only 8 of the 444

patients without MVO (1.8%) were complicated by an apical aneurysm (Tables 1 and 2).

Relationship of apical aneurysm formation to outcomes. When patients with MVO were divided into those with (n = 13) and those without (n = 33) an apical aneurysm, 5 of 13 MVO patients with an apical aneurysm (38.5%) experienced HCM-related death, including sudden death (n = 1), resuscitated cardiac arrest (n = 3), and appropriate implantable defibrillator interventions (n = 1). One of the 5 patients with adverse outcomes had no established major primary prevention risk factors for sudden death. Six of the 33 MVO patients without an apical aneurysm (18.2%) experienced HCM-related death. Two of the 6 patients with adverse outcomes had no established major primary prevention risk factors for sudden death. In multivariate models including MVO with or without an apical aneurysm and established major primary prevention risk factors for sudden death, apical aneurysm formation in patients with MVO strongly predicted HCM-related death (adjusted HR: 3.47, 95% CI: 1.38 to 8.73; p = 0.008) and the combined endpoint of sudden death and potentially lethal arrhythmic events (adjusted HR: 5.08, 95% CI: 1.97 to 13.05; p < 0.001). MVO without an apical aneurysm was also identified as an independent determinant of the combined endpoint of sudden death and potentially lethal arrhythmic events (adjusted HR: 2.43, 95% CI: 1.02 to 5.80; p = 0.045), but was not identified as an independent determinant of HCM-related death overall (adjusted HR: 1.72, 95% CI: 0.73 to 4.02; p = 0.213).

Discussion

In the current single-center patient cohort, MVO was confirmed in 9.4% of patients with HCM. Although no

Table 3 Predictors of HCM-Related Adverse Events in Univariate and Multivariate Analysis of MVO and Established Major Primary Prevention Risk Factors for Sudden Death

| Variables | No. of Patients | HCM-Related Death | | | | | Combined Endpoint of Sudden Death and Potentially Lethal Arrhythmic Events | | | | |
		No. (%) of Events	Crude Hazard Ratio (95% CI)	p Value	Adjusted Hazard Ratio (95% CI)	p Value	No. (%) of Events	Crude Hazard Ratio (95% CI)	p Value	Adjusted Hazard Ratio (95% CI)	p Value
Family history of sudden death											
Absent	429	51 (11.9)	1.00		1.00		38 (8.9)	1.00		1.00	
Present	61	13 (21.3)	1.68 (0.91-3.09)	0.096	1.35 (0.73-2.51)	0.338	10 (16.4)	1.82 (0.90-3.65)	0.094	1.41 (0.69-2.85)	0.344
Left ventricular wall thickness ≥30 mm											
Absent	475	59 (12.4)	1.00		1.00		43 (9.1)	1.00		1.00	
Present	15	5 (33.3)	2.89 (1.15-7.25)	0.024	3.26 (1.29-8.25)	0.012	5 (33.3)	3.56 (1.41-9.02)	0.007	4.35 (1.69-11.19)	0.002
Nonsustained ventricular tachycardia											
Absent	294	30 (10.2)	1.00		1.00		21 (7.1)	1.00		1.00	
Present	196	34 (17.3)	1.54 (0.94-2.53)	0.084	1.37 (0.83-2.25)	0.218	27 (13.8)	1.80 (1.02-3.19)	0.043	1.54 (0.86-2.76)	0.146
Unexplained syncope											
Absent	398	37 (9.3)	1.00		1.00		24 (6.0)	1.00		1.00	
Present	92	27 (29.3)	3.40 (2.07-5.58)	<0.001	3.23 (1.94-5.38)	<0.001	24 (26.1)	4.66 (2.64-8.20)	<0.001	4.32 (2.41-7.78)	<0.001
MVO											
Absent	444	53 (11.9)	1.00		1.00		37 (8.3)	1.00		1.00	
Present	46	11 (23.9)	2.17 (1.13-4.15)	0.020	2.23 (1.16-4.29)	0.016	11 (23.9)	3.16 (1.61-6.20)	<0.001	3.19 (1.62-6.29)	<0.001

CI = confidence interval; other abbreviations as in Table 1.

extensive clinical studies have been designed to determine the true prevalence of MVO in patients with HCM, MVO with an akinetic apical chamber has been considered to be a rare form of HCM, occurring in 1% of cases in the non-Asian population (5). According to a report from the United States, however, MVO was found in 8 of 62 patients (12.9%) with a diagnosis of HCM (18). In addition, MVO was present in 10.9% of patients with HCM in a 5-year study performed at an echocardiography laboratory in Italy (19). Furthermore, diastolic paradoxical jet flow across the obliterated left ventricular apex toward the base, suggestive of MVO and a discrete apical chamber, was present in 20 of 198 patients (10.1%) with HCM in a previous study (20). These variations in prevalence could be the result of racial/ ethnic differences, selection bias, underrecognition, misdiagnosis, or differences in the definitions of MVO. Despite being based on a highly selected population of patients with HCM from a single large tertiary referral center in Japan, the results of the current study have revealed novel epidemiological information about MVO in a relatively large HCM patient cohort.

A left ventricular apical aneurysm was identified in approximately one-fourth of HCM patients with MVO in the current study. Numerous previous case reports and studies have indicated that MVO is associated with an apical aneurysm in patients with HCM (5,7,8,16). Maron et al. (16) hypothesized that a left ventricular apical aneurysm and the associated regional myocardial scarring developed secondarily to increased left ventricular wall stress as a result of MVO and elevated intracavitary systolic pressures. Increased wall stress imposes an increased pressure load on the apical myocardium, increasing its oxygen demand, and impairs coronary flow through extravascular compression of the coronary artery, leading to chronic myocardial ischemia and aneurysm formation. The results of the current study, as well as those of previous studies, suggest the existence of a close overlap between MVO and an apical aneurysm in patients with HCM.

The presence of MVO was identified as an independent determinant of unfavorable outcomes in our analysis. In addition, apical aneurysm formation in patients with MVO more strongly predicted HCM-related adverse events. A recent study demonstrated a largely unfavorable clinical course in 28 HCM patients with an apical aneurysm. Twelve of the 28 patients (42.9%) either died of their disease or survived with severe adverse HCM-related events (16). Similarly, 5 of 13 patients (38.5%) with MVO and an apical aneurysm experienced HCM-related death in the present study. These results suggest that the higher mortality observed in patients with MVO might be due partly to aneurysm formation, which may develop secondarily to increased left ventricular wall stress as a result of MVO. Furthermore, the scarred rim of the aneurysm and the associated extensive areas of myocardial fibrosis have been regarded as arrhythmogenic substrates for the generation of malignant ventricular tachyarrhythmias (21,22). It is there-
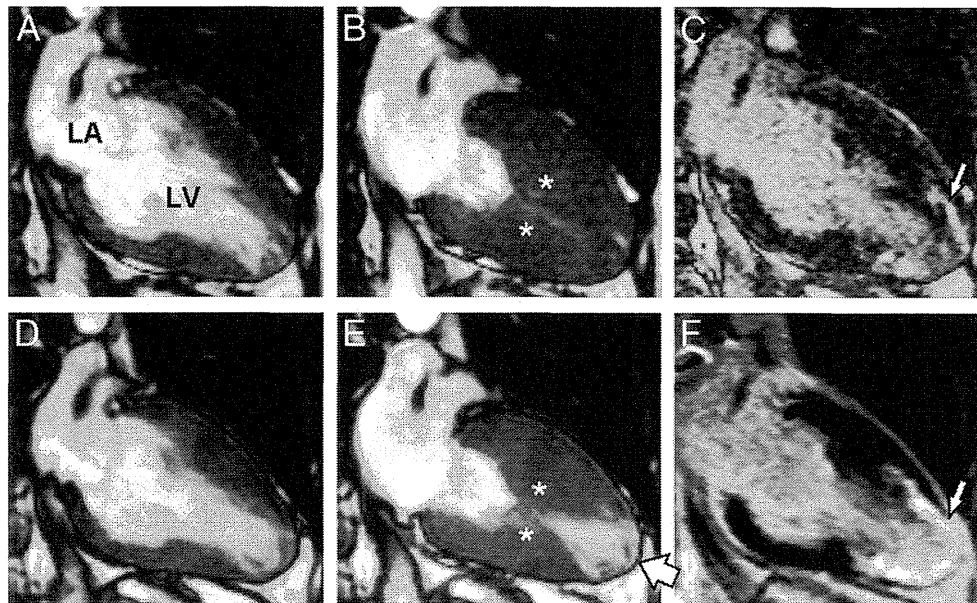
Figure 3 CMR Images From an HCM Patient in Whom an Apical Aneurysm Developed From MVO

Left ventricular long-axis 2-chamber cardiovascular magnetic resonance (CMR) cine images in end-diastole **(A)** and end-systole **(B)** from a 67-year-old HCM patient with MVO **(*)**. Identical imaging view in the same patient with gadolinium-diethylenetriaminepentaacetic acid already showing late gadolinium enhancement in the apex **(thin arrow, C)**. After 4 years, 2-chamber long-axis CMR images in end-diastole **(D)** and end-systole **(E)** demonstrating apical aneurysm formation **(thick arrow)**, which was associated with regional transmural late gadolinium enhancement of the aneurysmal wall **(thin arrow, F)**. LA = left atrium; LV = left ventricle; other abbreviations as in Figure 1.

fore not surprising that the majority of reported HCM-related events in patients with MVO and an apical aneurysm may be caused by ventricular arrhythmias (7,8). These observations suggest that the treatment of patients with MVO already complicated by an apical aneurysm should be modified to include primary prevention of sudden death with the use of an implanted defibrillator (16). In addition, MVO without an apical aneurysm was also associated with the risk of the combined endpoint of sudden death and potentially lethal arrhythmic events in this study. Furthermore, 2 MVO patients without an apical aneurysm and with no additional established major primary prevention risk factors for sudden death experienced adverse events. Additional clinical studies are needed to clarify whether the presence of MVO alone justifies the prophylactic use of an implantable defibrillator.

In this analysis, we also compared patients with MVO and those with OTO. Intriguingly, we found that the probability of HCM-related death in patients with MVO was similar to that in patients with OTO. Furthermore, the probability of the combined endpoint of sudden death and potentially lethal arrhythmic events in patients with MVO was higher than that in patients with OTO. This suggests that MVO could be as predictive of unfavorable outcomes as OTO because of increased wall stress, apical aneurysm formation, apical myocardial infarction, and myocardial scarring (16,21,22). Timely recognition of MVO might thus affect clinical practice decisions by

prompting consideration of gradient and wall stress relief with negative inotropic agents and/or therapeutic interventions. Numerous previous studies have demonstrated a reduction in intracavitary pressure gradients in HCM patients with MVO after dual-chamber pacing and myectomy (9–13). Successful surgical septal myectomy in OTO patients can completely abolish the gradients, leading to marked improvement of symptoms and outcomes (23). Surgical relief of MVO by extensive mid-left ventricular resection may thus similarly reduce HCM-related adverse events. However, patients with MVO had a lower left ventricular intracavitary gradient than those with OTO in our study cohort. In addition, MVO patients with an apical aneurysm had slightly lower midcavitary gradient than those without. This may be due partly to apical systolic dysfunction (hypokinesia, akinesia, or dyskinesia) and the midsystolic decrease in flow that can occur in patients with MVO (13,24). Lower gradients might lead to underestimation of the prognostic significance of MVO, resulting in inadequate medication and/or therapeutic interventions for the gradients of MVO. In comparison with OTO, MVO patients in this study used class I antiarrhythmic drugs less and had fewer invasive procedures to reduce the gradient of MVO, despite poor outcomes in the MVO patient group. Further studies are required to evaluate the actual severity of MVO and to determine the most appropriate treatment strategies for gradient reduction in patients with MVO.
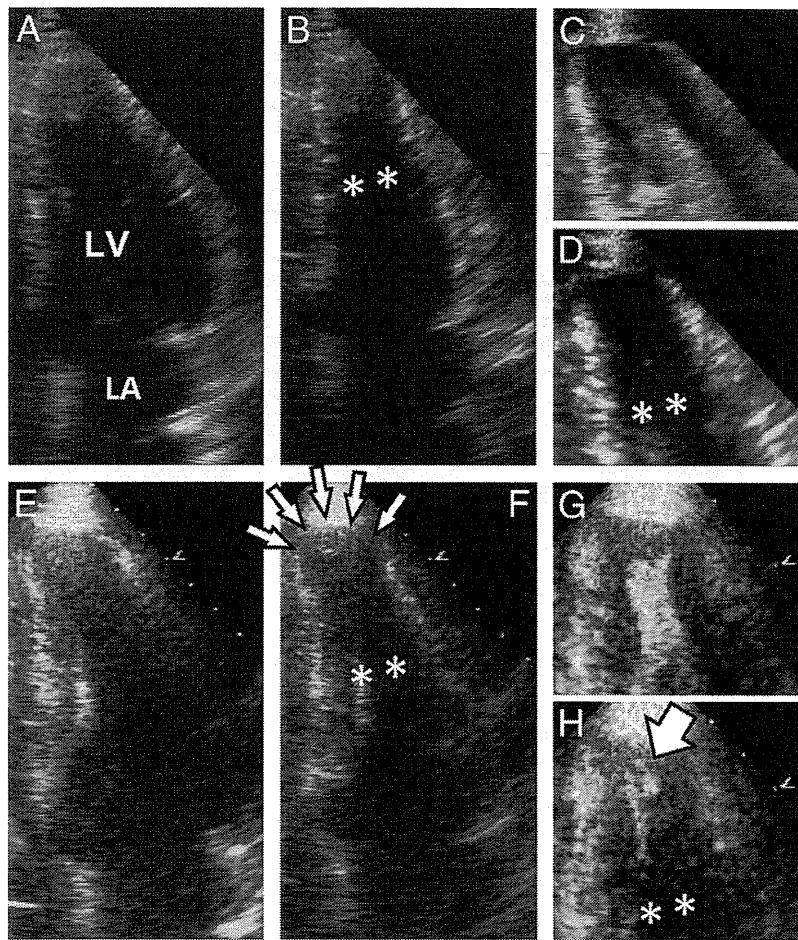
Figure 4   Echocardiographic Images of an HCM Patient in Whom an Apical Aneurysm Developed From MVO

Left ventricular apical 4-chamber views in end-diastole **(A)** and end-systole **(B)** in a 60-year-old HCM patient with MVO **(*)**. Contrast-enhanced 4-chamber views in end-diastole **(C)** and end-systole **(D)** showing no systolic pooling of contrast agent. Four-chamber views in end-diastole **(E)** and end-systole **(F)** in the same patient with MVO **(*)** after 4 years demonstrating apical aneurysm formation **(thin arrows)**. Contrast-enhanced 4-chamber views in end-diastole **(G)** and end-systole **(H)** showing apical systolic pooling of contrast agent **(thick arrow)**. Abbreviations as in Figures 1 and 3.

Study limitations. 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. In addition, some HCM patients were taking medication before their referral to our center, and the initial echocardiographic studies in some patients were thus performed while they were taking medication. Our results were thus likely to underestimate the prevalence and severity of MVO and OTO in this HCM patient cohort. The detection of apical hypertrophy and aneurysms in this study was based partly on transthoracic echocardiography, which has proven to be less reliable for detecting apical hypertrophy and aneurysms compared with the higher spatial resolution and detection capability of CMR imaging. In addition to CMR, contrast-enhanced echocardiography allows better delineation of the apical endocardium when apical acoustic windows are difficult to obtain (25). However, CMR and contrast-enhanced echocardiography were not performed in all MVO cases in this study, and our data were therefore likely to underestimate the true prevalence of apical hypertrophy and aneurysms in this cohort of patients with MVO.

Conclusions

In this HCM patient cohort, MVO was identified as an independent determinant of HCM-related death, especially the combined endpoint of sudden death and potentially lethal arrhythmic events. In addition, apical aneurysm formation in patients with MVO was more

Table 4	Baseline Characteristics of HCM Patients With MVO According to the Presence or Absence of an Apical Aneurysm		
	Patients With an Aneurysm (n = 13)	Patients Without an Aneurysm (n = 33)	p Value
Male	10 (76.9)	18 (54.5)	0.161
Age at diagnosis, yrs	50.5 ± 12.5	54.2 ± 15.5	0.447
Family history of sudden death	2 (15.4)	4 (12.1)	>0.999
Maximum left ventricular wall thickness, mm	19.1 ± 4.1	19.1 ± 4.5	0.991
Nonsustained ventricular tachycardia	7 (53.8)	7 (21.2)	0.041
Atrial fibrillation	3 (23.1)	8 (24.2)	>0.999
Unexplained syncope	5 (38.5)	7 (21.2)	0.276
NYHA functional class at diagnosis			0.513
I	3 (23.1)	10 (30.3)	
II	9 (69.2)	22 (66.7)	
III	1 (7.7)	1 (3.0)	
IV	0 (0.0)	0 (0.0)	
Progressive heart failure	2 (15.4)	4 (12.1)	>0.999
Stroke	1 (7.7)	4 (12.1)	>0.999
Pressure gradient at diagnosis, mm Hg	41.9 ± 12.1	47.5 ± 15.5	0.252
Treatments			
Beta-blockers	11 (84.6)	24 (72.7)	0.473
Calcium-channel blockers	2 (15.4)	12 (36.4)	0.286
Class I antiarrhythmic drugs	4 (30.8)	12 (36.4)	>0.999
All interventions combined	2 (15.4)	2 (6.1)	0.565
Warfarin	6 (46.2)	7 (21.2)	0.145
Follow-up duration, yrs	11.2 ± 10.3	10.1 ± 7.4	0.682

Values are n (%) or mean ± SD.
Abbreviations as in Table 1.

strongly associated with adverse outcomes. Our results suggest that longer periods of exposure to MVO and increased left ventricular wall stress might lead to apical aneurysm formation and clinically unfavorable consequences. The results also support the principle that the presence of MVO in patients with HCM has important pathophysiological implications. Timely recognition of MVO might thus prompt changes in clinical practice to allow for gradient relief and prophylactic defibrillator implantation and could also guide the challenge of improving the prognosis for HCM patients with MVO. Further studies are required to determine the most appropriate treatment strategies for patients with MVO.

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ORIGINAL ARTICLE

Long-term prognostic stratification by a combination of ^{123}I-metaiodobenzylguanidine scintigraphy and ejection fraction in dilated cardiomyopathy

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Abstract

Objective ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy is a useful tool for predicting the prognosis in patients with congestive heart failure; however, little is known regarding long-term prognostic evaluations. The aim of this study was to evaluate long-term prognosis in a roughly 10-year period, in dilated cardiomyopathy (DCM) by MIBG imaging, compared to other conventional functional parameters.

Methods Eighty-six DCM patients (50 ± 14 years of age, 57 males) underwent MIBG imaging, at 15 min and 4 h after tracer injection, from which the delayed heart to mediastinum ratio (H/M) and washout rate (WR) were obtained. The left ventricular ejection fraction (EF) and end-diastolic diameter (LVDd) were also measured by echocardiogram. All patients were followed up for 8–14 years, and the death event was investigated.

Results Kaplan–Meier curves revealed a poor prognosis only in the group above the third quartile of WR (=50%) (10-year prognosis, 35%); however, there were no statistically significant differences in prognosis among the other 3 groups (10-year prognosis, 75–84%). A Cox hazard univariate analysis selected WR ($p = 0.0004$), H/M ($p < 0.0001$), EF ($p = 0.0024$), and LVDd ($p = 0.0189$) as significant prognostic indicators. Multivariate analysis revealed the H/M ($p = 0.0023$) and EF ($p = 0.024$) to be an independent prognostic predictor. The 10-year prognosis of patients with both WR < 50% and EF > 30%; WR < 50% and EF < 30%; and both WR > 50% and EF < 30% were 89, 71, and 33%, respectively. These three groups were well stratified, significantly (log-rank test: $\chi^2 = 30.0$, $p < 0.0001$). However, even patients with WR ≥ 50% had few death events after 3 years following MIBG imaging.

Conclusions The MIBG parameter, delayed H/M or WR combined with the EF is a useful tool for the prediction of a long-term prognosis in DCM, which is superior to MIBG parameters alone. However, patients with WR > 50% but no event in a 3-year follow-up period should undergo an additional MIBG imaging for prognostic prediction.

Keywords ^{123}I-metaiodobenzylguanidine (MIBG) · Dilated cardiomyopathy · Washout rate

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Introduction

^{123}I-metaiodobenzylguanidine (MIBG) is an analog of guanethidine, and is taken up by uptake-1 as norepinephrine, followed by storage in adrenalin-related sympathetic nerve endings. Cardiac MIBG accumulation and washout reflect kinetics similar to norepinephrine [1]. Many previous reports have suggested that MIBG washout was increased, and myocardial delayed uptake was reduced in patients with heart failure, the severity of which was closely related to cardiac events or prognosis [2–4]. A multicenter study co-registered from Europe and the US has also confirmed the usefulness of MIBG for the prediction of prognosis in heart failure [5]. However, most prognostic studies using MIBG have been undertaken based on data with a follow up of less than 5 years, and these studies

defined only cardiac events as end points during the follow-up periods. We analyzed the data of all causes of mortality including cardiac events for a 10-year follow up after MIBG scintigraphy in patients with dilated cardiomyopathy (DCM), and assessed how MIBG contributed to the long-term prognostic evaluation in DCM patients, compared with other conventional parameters such as left ventricular ejection fraction (LVEF) and end-diastolic diameter.

Methods

Study population

Among 111 consecutive DCM patients who had undergone MIBG scintigraphy from 1993 to 1997, those patients who had death events or could be followed up for more than 8 years (n = 91) without death events were registered in this study. DCM was diagnosed by clinical history, ECG, chest roentgenogram, echocardiogram, or heart catheterization based on the Handbook for Diagnosis of the Japanese Ministry of Health and Welfare. Patients with severe chronic renal failure ($\geq$CKD stage IV, $n = 4$) and autonomic nervous system disorders ($n = 1$) were excluded. Finally, a total of 86 patients (67 $\pm$ 12 years old, 34 males) were enrolled in this study.

All patients were under hemodynamically compensated conditions at the time of MIBG imaging. Informed consent was obtained from each patient. The study protocol was approved by the institutional committee on human clinical investigations.

^{123}I-MIBG scintigraphy

After oral administration of 50 mg potassium iodide for thyroid block, planar scintigraphic imaging in the anterior view was obtained at 15 min (early) and 4 h (delayed) after the intravenous injection of 111 MBq of MIBG. Images were acquired using a single head gamma camera (DS7, Sophy Medical) equipped with a low-energy, high-resolution collimator. A preset time of 5 min was used for image acquisition, with a 159 $\pm$ 10 keV energy window.

For the quantitative analysis of MIBG, the delayed heart to mediastinum ratio (H/M) and washout rate (WR) for 4 h were calculated as described in a previous study [2].

Echocardiography

Echocardiography was performed at about the same time as MIBG scintigraphy. From the left ventricular short-axis image, the left ventricular end-diastolic diameter (LVDd)

and end-systolic diameter were measured and the LVEF was calculated using the standard method.

Patient follow up

The patients were followed up after the MIBG studies. No patient underwent heart transplantation. The end point was defined as death, from all causes. Sudden cardiac death was defined as death without definite premonitory symptoms or signs. Mortality data were gathered from the patient records in our hospital, telephone interviews, or correspondence by letter.

Statistics

The following variables were analyzed: age, gender, delayed H/M, WR, LVDd, and LVEF. Statistical values are shown as mean $\pm$ SD. Prognostic values were determined using a statistical software package (StatView, ver. 4.0). Univariate and multivariate Cox proportional hazards regression models were used to analyze the relations between all causes of death and the MIBG indices. Survival curves for patient subgroups were created by the Kaplan–Meier method to determine the time-dependent cumulative survival rate. These curves were compared using a 2-sample log-rank test. The mean values for the two groups were compared using an unpaired Student t test. A p value of less than 0.05 was considered statistically significant.

Results

The follow-up periods ranged from 0.12 to 14.4 years (average: 9.16 $\pm$ 4.21 years). Death events occurred in 26 patients (30%) due to 7 cardiac deaths (six heart failures and one fatal arrhythmia), 2 sudden deaths, 3 cerebrovascular diseases, 2 infectious diseases, one malignancy, one suicide, and one fatal complication of cardiac catheterization. The other 9 patients died of unknown causes.

All patients were divided into a Death group ($n = 26$) and an Alive group ($n = 60$), and the two groups were compared (Table 1). Older patients were included in the Death group ($p = 0.0019$). NYHA class was significantly higher in the Death group ($p = 0.011$), and the frequency of higher functional class was assigned in the Death group ($p = 0.0033$). The WR in the Death group was significantly higher than that in the Alive group ($p = 0.0012$). In addition, the H/M in the Death group was significantly lower than that in the Alive group ($p = 0.0001$). The LVEF and LVDd were lower and higher in the Death group, respectively ($p = 0.0017$, 0.0241, respectively).

**Table 1** Clinical characteristics of the Death and Alive groups

	Death	Alive	p value
No. of patients	26	60	
Age	56 ± 12	47 ± 15	0.0091
Male/female	22/4	44/16	NS
NYHA	2.15 ± 0.83	1.77 ± 0.53	0.011
I/II/III/IV	6/11/8/1	17/40/3/0	0.0033
Hypertension	2 (8%)	14 (23%)	NS
Diabetes	4 (15%)	8 (13%)	NS
Ventricular tachycardia	16 (62%)	24 (40%)	NS
Atrial fibrillation/flatter	4 (15%)	16 (27%)	NS
Medical treatments			
At the time of MIBG			
Digoxin	17 (65%)	32 (53%)	NS
Diuretics	24 (92%)	36 (60%)	0.0012
ACE	11 (42%)	27 (45%)	NS
β-blocker	6 (23%)	18 (30%)	NS
After MIBG			
ACE or ARB	21 (84%)	50 (86%)	NS
β-blocker	13 (50%)	41 (68%)	NS
WR (%)	43 ± 17	29 ± 18	0.0012
H/M	1.54 ± 0.21	1.79 ± 0.29	0.0001
LVEF (%)	24 ± 11	32 ± 11	0.0017
LVDd (mm)	68 ± 9	63 ± 9	0.0241

The frequency of diuretics in the Death group was higher than that in the Alive group ($p = 0.0012$). There were no significant differences in the frequency of either β-blocker or ACE inhibitor/angiotensin II receptor blocker (ARB) for medical therapy, either before or after the MIBG studies between the Death and Alive groups (Table 1).

With the end point defined as all causes of death, the survival curves are shown in Fig. 1. The threshold value of each parameter was determined as an optimal cutoff point statistically obtained by log-rank test between the two classified groups. The cutoff point was 30%, 50% and 1.45 for ejection fraction (EF), MIBG WR, and H/M, respectively. These curves show that those patients with either an EF less than 30%, a WR of more than 50% and a H/M less than 1.45 had a poor prognosis($p = 0.0014$, $p < 0.0001$, $p = 0.0001$, respectively). All patients were quartered via LVEF and WR values to obtain the mortality in each classified group. The 10-year mortalities in each classified group for LVEF and WR are shown in Fig. 2. The second quartile (30% in LVEF) and the third quartile (50% in WR) are appropriate cutoff values for death events.

The prognostic value of MIBG and echocardiographic parameters with the Cox hazard univariate regression model for all causes of death is shown in Table 2. The four variables shown were all significant prognostic parameters. Among those variables, Cox hazard multivariate regression

Fig. 1 Kaplan–Meier curves stratified by EF (**a**), WR (**b**) and H/M (**c**) with the end point defined as all causes of death. These curves show that patients with an EF less than 30%, a WR of more than 50% or an H/M less than 1.45 had poor prognoses
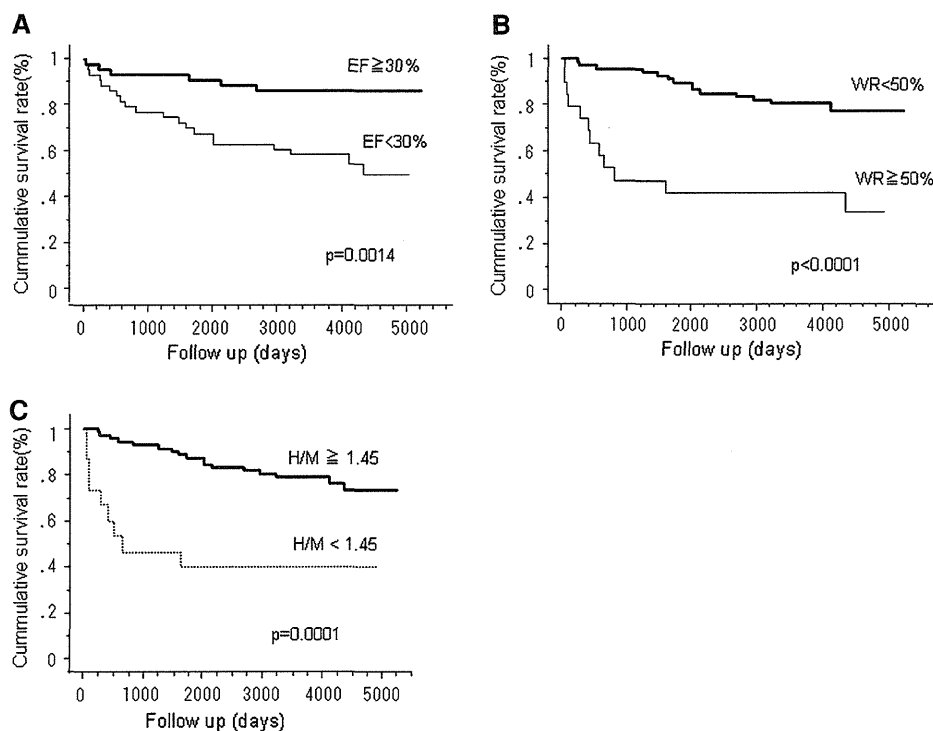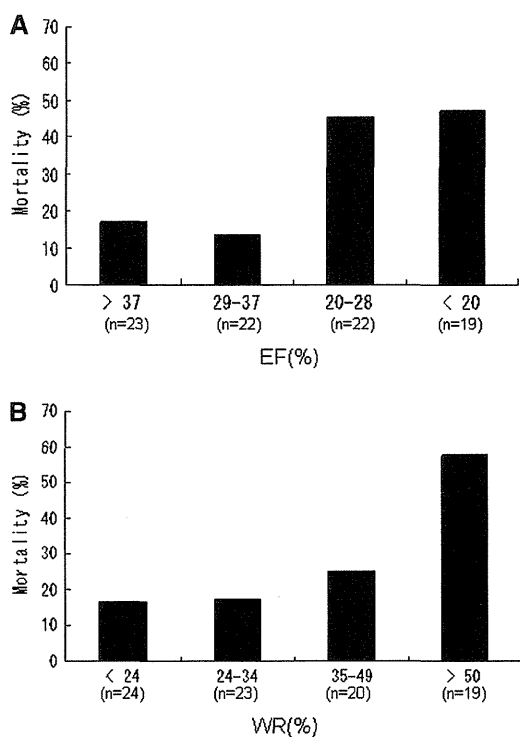
Fig. 2 The 10-year mortality in four groups, classified via LVEF (a) and WR (b). The second quartile (30%) in LVEF and the third quartile (50%) in WR were appropriate cutoff values for cardiac death

Table 2 Cox hazard univariate (a) and multivariate (b) regression analysis

Variables	χ^2	Hazard ratio (95% CI)	p value
(a)			
NYHA	7.98	2.529 (1.3283–4.814)	0.0047
LVDd	8.24	1.063 (1.020–1.109)	0.0041
LVEF	9.23	0.940 (0.904–0.978)	0.0024
WR	12.94	1.041 (1.018–1.064)	0.0003
H/M	16.43	0.044 (0.010–0.199)	<0.0001
(b)			
LVEF	4.28	0.960 (0.923–0.998)	0.039
H/M	11.18	0.059 (0.011–0.309)	0.0008

analysis revealed that the H/M and EF were independent prognostic parameters for all causes of death ($\chi^2 = 18.43$, $p < 0.0001$).

Kaplan–Meier curves stratified by a combination of WR and EF values are shown in Fig. 3: WR < 50% and EF ≥ 30% (group A, $n = 36$); WR < 50% and EF < 30% (group B, $n = 35$); and WR ≥ 50% and EF < 30% (group C, $n = 15$). No patient was categorized into a group with WR ≥ 50% and EF ≥ 30%. The 10-year survival rates for patients in groups A, B, and C were 89, 71, and 33%, respectively. Patients in group A had a good prognosis. The
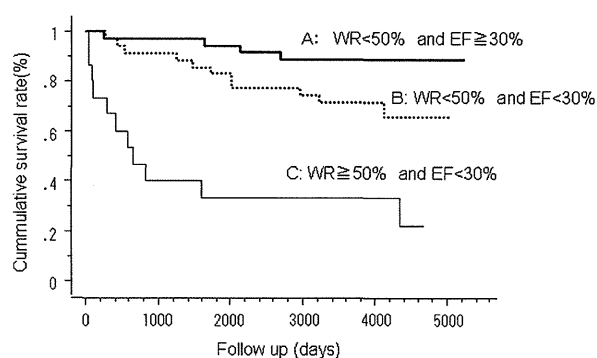

Fig. 3 Kaplan–Meier curves stratified by a combination of WR and EF values: WR < 50% and EF ≥ 30% (group A, $n = 36$); WR < 50% and EF < 30% (group B, $n = 35$); WR ≥ 50% and EF < 30% (group C, $n = 15$). These three curves are well differentiated ($\chi^2 = 30.0$, $p < 0.0001$)

three curves are well stratified significantly ($\chi^2 = 30.0$, $p < 0.0001$). However, even patients in group C had few death events after 3 years following MIBG imaging.

After excluding patients with unknown causes of death ($n = 9$), we evaluated the prognostic significance for cardiac death including sudden death ($n = 9$). Multivariate analysis revealed that only WR was an independent prognostic indicator ($\chi^2 = 9.00$, $p = 0.0027$). Kaplan–Meier curves divided by a threshold value of 50% in WR and 1.45 in H/M were significantly different ($\chi^2 = 17.30$, $p < 0.0001$ and $\chi^2 = 11.3$, $p = 0.0008$, respectively). EF was not a prognostic indicator for cardiac death in either the Cox hazard regression analysis or Kaplan–Meier analysis (Fig. 4).

Discussion

The present study indicated that MIBG scintigraphy is a useful prognostic tool over a 10-year follow-up period in patients with DCM. Another conventional functional parameter, the EF, was also an independent prognostic indicator, which had a less significant prognostic value than the H/M in MIBG. However, the combination of two prognostic parameters was found to be an independent prognostic indicator, as determined by multivariate analysis. In particular, one of the parameters of MIBG, the WR, when combined with the EF was a strong prognostic marker (Fig. 3), and is very useful in the stratification of disease severity. Patients with WR ≥ 50% and EF < 30% had particularly poor prognoses.

Kaplan–Meier curves show that frequent death events occurred during the first 3 years in patients with higher WR values (≥50%). In contrast, these events occurred gradually over the 10-year study period in patients with low EF values. This result indicated that MIBG data are especially

Fig. 4 Kaplan–Meier curves
stratified by the EF (**a**), WR
(**b**) and H/M (**c**) with the end
point defined as cardiac death.
The curves show that the
patients with a WR of more than
50% and H/M less than 1.45 had
poor prognoses. However, the
EF does not exhibit prognostic
significance, according to the
Kaplan–Meier analysis
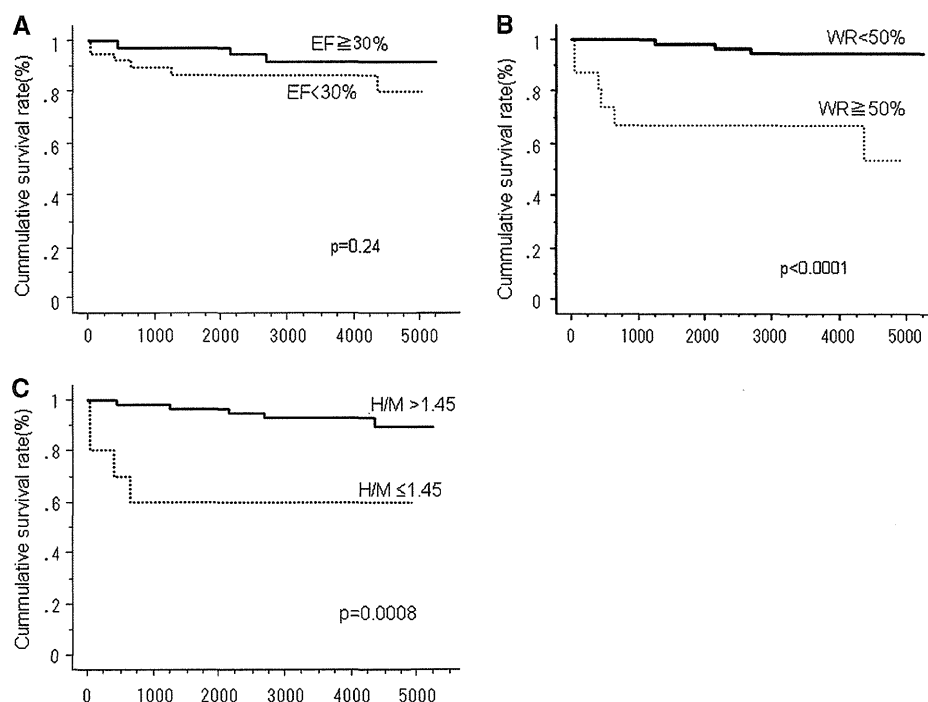
useful in predicting short-term death events within several
years, while the EF reflects the long-term prognosis, but is
less useful in predicting short-term prognosis. Even
patients with higher WR values (≥50%) had few death
events after 3 years following MIBG imaging, and the
reason for this is not clear. However, patients with effective
initial medical therapy may survive even longer than
patients with higher WR values. Akutsu et al. [6] reported a
10-year long-term prognostic evaluation in patients with
ventricular tachycardia, where the first 3-year survival
curve with lower H/M also showed frequent cardiac events,
but very few events during the rest of the follow-up peri-
ods. The survival curve pattern was very similar to our
study. A recent study revealed that patients with no cardiac
event even after 2 years of follow up should undergo
MIBG repetitively for prognostic prediction [7], which is a
partially supportive result. In this respect, patients with
WR > 50% who survive for 3 years should undergo
MIBG, and should be re-evaluated regarding prognosis.

We also investigated the threshold value of the param-
eters for predicting prognosis. When WR was stratified into
4 classes, only the fourth most severe group (>50%) had a
higher death event rate, whereas the other 3 groups were
comparable. These data suggested that MIBG may pri-
marily detect poor prognostic cases, the patients of which
die within several years. Another important point is the
good prognosis observed for patients with higher EF values
(>30%), regardless of WR value. Many enrolled patients
underwent MIBG imaging before complete medical ther-
apy in this clinical setting, because 28 and 44% of the

patients took β-blockers and ACE, respectively, before the
imaging, while another 35 and 39% of the patients,
respectively, took these medical treatments (total: 63 and
83%) after the imaging; therefore, proper medical treat-
ment was certainly performed for these patients during the
follow-up period after MIBG imaging. Under this condi-
tion, patients with relatively higher EF values (>30%) are
less likely to have death events over the 10-year follow-up
period.

In the current study, a composite end point including all
causes of mortality was used, which is not a direct cardiac
end point. An important advantage of all-cause mortality,
however, is the fact that it is not affected by verification
bias [8]. Furthermore, most deaths in adults are linked to
cardiovascular disease. All causes of mortality is, therefore,
a commonly used end point, which allows a comparison of
the current results to previous investigations [9–12].

We also assessed the prognostic significance for only
cardiac as the cause of death. As for all causes of death,
WR was also a good prognostic indicator for cardiac death.
However, EF was not a prognostic indicator for only car-
diac death. The EF may not exhibit a direct influence on
cardiac death. Actually, the Kaplan–Meier curve for the
lower EF group descends gradually in a stepwise manner
over the 10-year follow-up period (Fig. 1a). The lower EF
group might tend to involve, rather the non-cardiac cause
of death events.

Plasma BNP concentration is also a good prognostic
parameter among heart failure patients [13, 14]. A com-
bination of the H/M in MIBG and plasma BNP is reported

to yield greater prognostic information than that from MIBG alone within 16 months [15]. However, it is not clear whether BNP is useful for long-term prognosis in these patients. We did not obtain BNP data in our present study, because no BNP sampling was routinely performed at the beginning of the study in the period from 1993 to 1997. Further investigation is needed to clarify the usefulness of plasma BNP level, in combination with MIBG parameters for long-term prognosis in DCM patients.

A decreased MIBG WR is often observed in patients who have received an effect on cardiac function due to complete medical therapy, indicating a prolonged survival rate [16, 17]. However, we enrolled patients who underwent MIBG imaging under a compensate state of heart failure, but with both complete and non-complete medical therapies. Therefore, the events would depend on additional medical therapy received after MIBG imaging, although medical treatment was altered by patient cardiac status in a long-term follow-up period. We did not include heart failure or fatal arrhythmic events; thus, the final event may strongly depend on the MIBG parameters, regardless of medical therapy, according to the present study results.

Conclusion

The MIBG parameter, delayed H/M or WR combined with the EF is a useful tool for the prediction of a long-term prognosis in DCM, which is superior to MIBG parameters alone. However patients with WR > 50% but no event in a 3-year follow-up period should undergo an additional MIBG imaging to predict the prognosis.

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ORIGINAL ARTICLE

Arrhythmia/Electrophysiology

Clinical Outcome in Patients With Paroxysmal or Persistent Atrial Fibrillation Receiving Bepridil

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Background: It is unknown whether bepridil improves cardiovascular events in atrial fibrillation (AF) patients, so this study evaluated the clinical outcome in paroxysmal or persistent AF patients receiving bepridil.

Methods and Results: We conducted a cohort study of 284 consecutive patients who received bepridil for AF (25% female, 59±13 years) with a median follow-up period of 17 months (4–157 months). A total of 135 (48%) patients had structural heart disease, and 231 patients (81%) had previously received class I or class III antiarrhythmic drugs. The cumulative rates for cardiovascular events were 2.4%, 8.1%, and 10.1% at 1, 3, and 5 years, respectively. The cumulative rates for a composite of mortality, cerebral infarction, systemic embolism, major bleeding and heart failure were 9.7%, 18.2%, and 29.6% at 1, 3, and 5 years, respectively. The probability of progression to permanent AF was 23.5% at 5 years. Sudden death occurred in a patient with a prior myocardial infarction who was taking 200 mg daily, and torsade de pointes (Tdp) occurred in two patients without structural heart disease taking 200 mg daily. Excessive corrected QT interval prolongation (>0.50 s) was observed when plasma concentrations were higher than 800 ng/ml.

Conclusions: Bepridil might not improve the clinical outcome in refractory AF patients. Bepridil-related adverse events, including QT prolongation and Tdp, occurred in a dose- and concentration-dependent manner. (*Circ J* 2011; **75:** 1334–1342)

Key Words: Atrial fibrillation; Bepridil; Mortality; Pharmacokinetics; Torsade de pointes

Atrial fibrillation (AF) is the most clinically prevalent tachyarrhythmia, and the incidence of AF increases with advancing age.[1,2] AF occurs in patients with a variety of cardiovascular diseases, as well as in those without structural heart disease. The development of AF results in worsening hemodynamics in patients with heart failure or left ventricular (LV) hypertrophy, causing an uncontrolled heart rate with shortened filling time and the provocation of tachycardiomyopathy. The absence of the atrial kick and an irregular ventricular rhythm leads to a decrease in cardiac output.[3] AF is a potential risk factor for stroke, heart failure and death,[4–6] and it impairs quality of life.[7]

The therapeutic goal for AF patients is reducing symptoms and preventing the severe complications associated with AF.[8] In the past, most studies assessing the efficacy of antiarrhythmic drugs have focused primarily on the incidence of conversion to sinus rhythm or the prevention of AF, rather than on more global endpoints.[9] However, it remains unclear whether using antiarrhythmic drugs to maintain sinus rhythm is linked to improved clinical outcomes in AF patients. Recently, AF treatment assessment has tended toward evaluating clinical outcomes, including mortality and cardiovascular morbidity, or quality of life since achieving rhythm. To date, there have been no randomized clinical trials comparing rate vs. rhythm control that indicate that rhythm control improve mortality and cardiovascular events.[10–13] Interestingly, a post-hoc analysis of the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) study suggested that antiarrhythmic drugs are not associated with improved survival because the benefits of sinus rhythm are offset by the drugs' adverse effects.[14] It was concluded that antiarrhythmic drugs have modest effects on restoring and maintaining sinus rhythm in AF and have adverse pro-arrhythmic and extracardiac side effects. The decision to use antiarrhythmic drugs should be based on safety rather than efficacy considerations, such as the maintenance of sinus rhythm.[8,9]
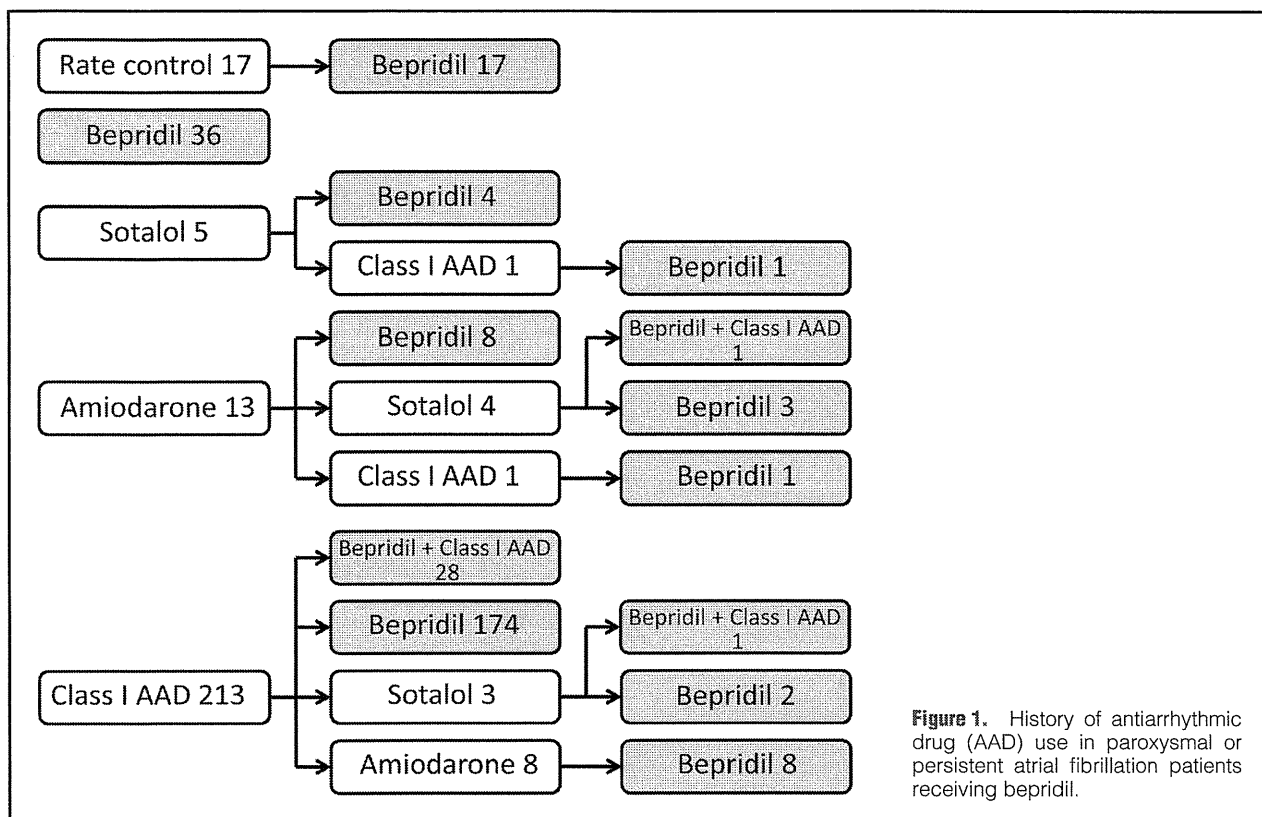
Figure 1. History of antiarrhythmic drug (AAD) use in paroxysmal or persistent atrial fibrillation patients receiving bepridil.

Bepridil is classified as a calcium-channel blocker and has been used as an antianginal drug in Europe and North America.[15] Bepridil produces a lidocaine-like fast kinetic block of the inward sodium current, blockade of several outward potassium currents and inhibition of sodium–calcium exchange.[15,16] In Japan, bepridil is used as an antiarrhythmic drug because its unique electrophysiological properties make it behave like class I, class III and class IV antiarrhythmic drugs. Previous reports have shown the efficacy of bepridil in AF patients who were refractory to class I antiarrhythmic drugs.[17–20] Additionally, many clinical studies, including retrospective and prospective evaluations, have shown bepridil's efficacy in converting persistent AF to sinus rhythm.[17,19–24] However, bepridil has serious adverse effects, such as sudden cardiac death, torsade de pointes (Tdp) with QT prolongation and excessive bradyarrhythmia.[24,25]

To date, there have been few reports concerning outcome, including cardiovascular events and safety issues, in AF patients during long-term bepridil therapy. Bepridil has complex pharmacokinetic properties,[26,27] and the optimal safe dose in AF patients has not yet been fully determined. The aim of this study was to evaluate the clinical outcome of patients with paroxysmal or persistent AF who received bepridil.

Methods

Subjects

We conducted a cohort study of 284 consecutive patients who received bepridil for paroxysmal or persistent AF at Tokyo Women's Medical University Hospital between February 1988 and April 2010. Among them, 231 patients (81%) had received class I or class III antiarrhythmic drugs prior to bepridil therapy, and 220 patients were switched to bepridil

because class I and class III antiarrhythmic drugs failed to prevent AF recurrence or restore sinus rhythm. An additional, 11 patients were switched from amiodarone to bepridil because of the pulmonary toxicity of amiodarone. The remaining 53 patients received bepridil as a first-line antiarrhythmic drug. A total of 30 patients (11%) received combined therapy with bepridil and a class I antiarrhythmic drug (Figure 1). The protocol was approved by the Institutional Review Board of Tokyo Women's Medical University.

Drug Dosing

Patients were given oral bepridil at a dose of 100–200 mg daily. In the case of combination therapy with another antiarrhythmic drug, patients were initially given 50 mg daily. The maintenance dose of 50–200 mg daily was adjusted, and the efficacy and side effects of bepridil were monitored.

Among the 30 patients who received combination therapy with bepridil and a class I antiarrhythmic drug, 6 were prescribed 50 mg of bepridil daily, 13 patients were prescribed 100 mg daily, 4 patients were prescribed 150 mg daily and 7 patients were prescribed 200 mg daily.

Classification of AF

Paroxysmal AF is characterized by recurrent episodes alternating with sinus rhythm. Episodes that spontaneously reversed within 7 days without antiarrhythmic drug therapy or electrical cardioversion were classified as paroxysmal, and those that either lasted longer than 7 days or required pharmacological or electrical cardioversion for termination were classified as persistent. If sinus rhythm could not be sustained despite these treatments or if the patient and physician decided to allow AF to continue without further efforts to restore sinus rhythm, the case was classified as permanent AF;[8,28] that is,

Table 1. Baseline Characteristics of the Patients With AF	
n	284
Age (years)	59±13
Female	71 (25%)
Echocardiographic characteristics	
Left atrial size (mm)	39±9
Fraction shortening	0.33±0.09
Type of AF	
Paroxysmal	263 (93%)
Persistent	21 (7%)
Structural heart disease	
Coronary artery disease	39 (14%)
Nonischemic cardiomyopathy	48 (17%)
Valvular heart disease	25 (9%)
Congenital heart disease	18 (6%)
Other	5 (2%)
History of congestive heart failure	63 (22%)
Coexisting conditions	
Hypertension	80 (28%)
Diabetes	39 (14%)
Previous stroke or TIA	35 (12%)
eGFR <60 ml·min^{-1}·1.73 m^{-2}	49 (17%)
CHADS$_2$ score	
0	124 (44%)
1	88 (31%)
2	41 (14%)
3	24 (9%)
≥4	7 (2%)
Concomitant medications	
Warfarin	152 (54%)
Aspirin	108 (38%)
ACE inhibitor/ARB	126 (44%)
β-blocker	143 (50%)
Calcium-channel blocker	69 (24%)
Digoxin	77 (27%)
Statin	38 (13%)
Class I antiarrhythmic drug	30 (11%)

Values are n (%) or mean±SD.
AF, atrial fibrillation; TIA, transient ischemic attack; eGFR, estimated glomerular filtration rate; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.
eGFR was calculated using the Modification of Diet in Renal Disease formula.[30]

the term 'permanent AF' was an expression of the patient's intent rather than a description of the pathophysiology.

Definition of Structural Heart Disease

Structural heart disease consisted of the following apparent cardiac disorders: LV systolic dysfunction and/or marked LV dilatation unless secondary to severe valve regurgitation; LV hypertrophy; coronary artery disease; right heart disease with right ventricular dilation of at least moderate severity; moderate or severe tricuspid regurgitation or pulmonary hypertension; left-sided valvular disease; and congenital heart disease. Coronary artery disease was defined as positive stress test findings, coronary angiography demonstrating at least 75% stenosis or coronary spastic angina documented by acetylcholine provocation test, a history of prior myocardial infarction (MI), or a history of revascularization proce-

dures. Valvular and congenital heart diseases were defined according to the angiographic, hemodynamic or echocardiographic findings or a history of valvular or congenital cardiac surgery. Atrial or mitral regurgitation was defined as valvular disease when we identified greater than moderate regurgitation on color flow Doppler echocardiography. Nonischemic cardiomyopathies were defined as ventricular myocardial abnormalities in the absence of coronary artery disease or valvular, pericardial or congenital heart disease.

Follow-up

Follow-up data were obtained at routine visits to our institution (every 1–3 months). Patients were followed until the end of the follow-up period (August 31, 2010), until death, until bepridil was discontinued, or until they were lost to follow-up. Information about deceased patients was obtained from medical records, family members, patients' general practitioners and the hospitals to which they had been admitted.

Baseline 12-lead ECG, chest X-ray, echocardiography, and renal and liver function tests were performed for most patients before bepridil therapy. 12-lead ECG was performed at each routine visit and several times during therapy. The 12-lead ECGs were recorded at standard gain (10 mm/mV) and speed (25 mm/s). Heart rate, QRS duration, QT and corrected QT (QTc) intervals were measured by 2 independent investigators (A.S. and M.N.). The QT interval was measured from the onset of the QRS interval to the end of the T wave in all the leads for which the end of the T wave could be clearly defined. The QTc value was measured using Bazett's formula. After May 2007, blood samples for plasma drug concentrations were also drawn if patients gave informed consent. The plasma bepridil concentration was measured by high-pressure liquid chromatography assay.

Endpoints

The primary endpoint was the time to first cardiovascular event and was a composite of the following: cardiovascular death, non-fatal MI, hospitalization for unstable angina, hospitalization for heart failure, hospitalization for stroke, hospitalization for other cardiovascular disease, documented Tdp, sustained ventricular tachycardia or fibrillation, and syncope/presyncope, which were considered because they are potential symptoms of Tdp. Cardiovascular death was defined as death due to myocardial or cerebral infarction or documented sudden cardiac death. Unstable angina was defined according to the Braunwald criteria.[29] Heart failure was defined on the basis of symptoms, such as dyspnea, clinical signs, such as rales or ankle edema, and the need for treatment with diuretics, vasodilators, or inotropics. Stroke was defined as a new focal neurological deficit of vascular origin lasting more than 24 h. Stroke was further classified as the result of intracranial hemorrhage, ischemia (if results of computed tomography or magnetic resonance imaging were available), or uncertain cause. Other cardiovascular events included peripheral artery diseases, dissecting aneurysm of the aorta, and aortic aneurysm rupture. The main secondary endpoint was a composite of the following: total mortality, symptomatic cerebral infarction, systemic embolism, major bleeding, or hospitalization for heart failure, which was used as the primary outcome minus physical/psychological disability (hard endpoint) in the J-RHYTHM (Japanese Rhythm Management Trial for Atrial Fibrillation) study.[13] Another secondary endpoint was the time to diagnosis of permanent AF.