Clinical Investigations

Risk of Sudden Death in End-Stage Hypertrophic Cardiomyopathy

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ABSTRACT

Background: It remains unclear whether end-stage hypertrophic cardiomyopathy (HCM) is associated with as high a rate of sudden death as occurs among HCM patients with preserved left ventricular (LV) systolic function. The purpose of this study was to evaluate the incidence of sudden death among patients with end-stage HCM and to identify high-risk end-stage patients.

Methods and Results: A total of 490 consecutive patients with HCM, who were diagnosed and followed-up at our hospital, were analyzed retrospectively. End-stage HCM was defined by an LV ejection fraction <50% on echocardiography during follow-up. Among the 490 HCM patients, 43 patients (8.8%) were diagnosed as having end-stage HCM during a mean follow-up period of 12 ± 7 years after the initial diagnosis. During a mean follow-up period of 5 ± 3 years after progression to end-stage HCM, sudden death occurred in 21 of 43 patients (47%). Cox proportional hazards analysis identified syncope as an independent predictor of sudden death (hazard ratio = 6.15; 95% confidence interval, 2.40-15.75; $P < .001$).

Conclusions: This study demonstrated that patients with end-stage HCM have a high incidence of sudden death. Therefore, it is suggested that an aggressive therapeutic strategy to counter sudden death should be considered for patients with end-stage HCM. (*J Cardiac Fail 2011;17:459–464*)

Key Words: Heart failure, epidemiology, prognosis, syncope.

In most patients with hypertrophic cardiomyopathy (HCM), left ventricular (LV) systolic function is normal or supernormal, whereas abnormalities of LV relaxation and filling are identified in approximately 80%.[1] A distinctive terminal phase of this disease, resembling the morphological and functional features of dilated cardiomyopathy, is observed in 2.4 to 15% of patients with symptomatic HCM.[2–8] Recently, it was reported that a common feature of end-stage HCM is progressive systolic dysfunction, which is superimposed on preexisting diastolic dysfunction and is accompanied by LV dilatation, ventricular wall thinning, or both in approximately 50% of patients.[9] Development of such LV systolic dysfunction in HCM patients has serious clinical implications because it is associated with high rates of heart failure death and sudden death.[9] Although sudden death has been recognized as a prominent and devastating consequence of HCM, it has been unclear whether sudden death is as common in end-stage disease as it is among HCM patients with preserved LV systolic function.[1,10–12] Furthermore, the risk factors for sudden death in HCM patients who progress to end-stage disease are not fully understood. Accordingly, the purpose of this study was to evaluate the incidence of sudden death among patients with end-stage HCM and to identify a high-risk subgroup of end-stage patients.

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Methods

Study Population and Diagnostic Criteria

A total of 490 consecutive patients with HCM (334 with nonobstructive HCM and 156 with obstructive HCM; the mean age at

diagnosis: 46 ± 15 years) were diagnosed and followed-up at Tokyo Women's Medical University Hospital (Tokyo, Japan), which is a referral center, between 1980 and 2005.[13] We retrospectively analyzed the incidence and clinical characteristics of end-stage HCM during follow-up after the initial diagnosis of HCM. We also analyzed cardiovascular mortality in patients with end-stage HCM during follow-up after the diagnosis of end-stage disease. A diagnosis of HCM was based on echocardiographic evidence of LV hypertrophy (wall thickness >15 mm) in the absence of any other cardiac or systemic disease capable of producing similar hypertrophy.[1,8] Exclusion criteria were a history of hypertension or coronary artery disease and severe congestive heart failure. We also excluded patients who were diagnosed as having end-stage HCM at their first evaluation because it is difficult to distinguish end-stage HCM from idiopathic dilated cardiomyopathy in such patients.[14] The present study was conducted in accordance with the Declaration of Helsinki.

Definitions

End-stage HCM was defined by the detection of LV cavity enlargement and an LV ejection fraction (LVEF) <50% on echocardiography without a history of surgical or ablative septal reduction therapy during follow-up of HCM.[4–7] LV outflow tract obstruction from systolic anterior motion of the mitral valve with septal contact was considered to be present when the peak instantaneous gradient was estimated to be at least 30 mm Hg by continuous-wave Doppler echocardiography under resting conditions.[1,8] The diagnostic criteria for apical hypertrophy included the detection of asymmetric LV hypertrophy (predominantly confined to the LV apex) and an apical wall thickness ≥15 mm on 2-dimensional echocardiography or cardiovascular magnetic resonance imaging.[15]

Cardiovascular morbidity was defined as stroke, heart failure, and syncope. Cardiovascular death was defined as sudden death, heart failure–related death, stroke-related death, and heart transplantation. Sudden death included both sudden cardiac death and nonfatal cardiac arrest, including appropriate implantable cardioverter-defibrillator (ICD) interventions, such as antitachycardia pacing therapy and shock therapy. Heart failure–related death included support by an LV assist device and heart transplantation.[16] Nonsustained ventricular tachycardia (VT) was defined as one or more runs of 3 or more consecutive ventricular extrasystoles at a rate of >120 minutes and lasting for <30 seconds.[8]

Echocardiography

Echocardiographic studies were performed using commercially available ultrasound equipment. Complete M-mode, 2-dimensional, and Doppler studies were performed, in the left lateral decubitus or supine position via the standard parasternal, apical, and subcostal approaches. The severity and distribution of LV hypertrophy was assessed in the short-axis view by dividing the LV wall into 4 segments (anterior septum, posterior septum, anterolateral wall, and posterior wall) at the level of the mitral valve and also at the papillary muscles. Maximal LV wall thickness was defined as the greatest thickness in any single segment. LV outflow tract obstruction, caused by systolic anterior motion of the mitral valve with septal contact, was considered to be present when the estimated peak instantaneous gradient was ≥30 mm Hg during based on continuous-wave Doppler echocardiography under basal (resting) conditions. The ejection fraction was calculated from 2-dimensional echocardiographic images by the modified Simpson's formula.

Statistical Analysis

Analyses were performed with SAS ver. 9.1 software (SAS Institute, Cary, NC). Data are presented as the mean ± SD or as frequencies. Student's *t*-test was employed to compare with respect to normally distributed continuous variables between 2 groups, whereas the chi-square test was used to compare nominal variables. Cumulative event-free curves were drawn by the Kaplan-Meier method, and differences between curves were determined with the log-rank test. Multivariate Cox proportional hazards analysis with stepwise selection of variables was applied to evaluate the influence of syncope at the time of diagnosing end-stage HCM on total death, heart failure death, and sudden death. The influence of profile, interaction, and collinearity in the models were examined by regression diagnostic analysis. Two-tailed *P* values <.05 were considered to indicate a statistically significant difference.

Results

Incidence and Baseline Characteristics

Among 490 patients with HCM, 43 (8.8%) patients showed progression to end-stage disease during a mean follow-up period of 12 ± 7 years after the initial diagnosis of HCM. The annual incidence of end-stage HCM was 0.73%. Among these 43 patients, 28 patients (65%) had an LVEF <50% and left ventricular diastolic dimension (LVDD) ≥55 mm, whereas the remaining 15 patients (35%) only had an LVEF <50%. The patients with end-stage HCM were aged 44 ± 15 years (range, 6 to 68 years) at the initial diagnosis of HCM and 56 ± 12 years (range, 22 to 78 years) at the diagnosis of end-stage HCM (Table 1). Among these 43 patients, the incidence of a familial HCM and a family history of sudden death was 37% and 28%, respectively. The incidence of syncope at the diagnosis of end-stage HCM was 23% (10/43 patients). At the initial diagnosis of HCM, 25 patients (58%) had asymmetric septal hypertrophy, 11 (26%) had concentric hypertrophy, and 7 (16%) had apical hypertrophy. Interestingly, no patient with obstructive hypertrophy showed progression to end-stage HCM during the present study. At the diagnosis of end-stage HCM, mean LVDD and LVEF were 59 ± 6 mm and 36 ± 10%, respectively. Among the 43 patients with end-stage HCM, 30 patients (70%) were being treated with β-blockers, 35 patients (81%) with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and 26 patients (60%) with spironolactone. Also, amiodarone was administered to 21 patients (49%) during follow-up. During a mean follow-up of 5 ± 3 years after the diagnosis of end-stage HCM, 13 (30%) patients developed persistent atrial fibrillation, and 25 patients (58%) had nonsustained VT. At the time of diagnosing end-stage HCM, an ICD had been implanted in 13 patients (30%), with the indication for implantation being primary prevention in 8 patients and secondary prevention in 5 patients. Also, after progression to end-stage HCM, 3 patients received ICDs for the primary prevention of sudden death.

Cardiovascular Mortality

During a mean follow-up period of 5 ± 3 years after progression to end-stage HCM, overall-related death occurred

Table 1. Baseline Characteristics of End-stage HCM Patients

Variables	End-stage HCM (n = 43)
Age at initial diagnosis of HCM, y	44 ± 15
Age at diagnosis of end-stage HCM, y	56 ± 12
Male	34 (79%)
Family history of HCM	16 (37%)
Family history of sudden death	12 (28%)
HCM-related morbidity at diagnosis of end-stage HCM	
Stroke	11 (26%)
Heart failure	10 (23%)
Syncope	10 (23%)
Chronic atrial fibrillation at diagnosis of end-stage HCM	13 (30%)
Nonsustained VT at diagnosis of end-stage HCM	25 (58%)
VF at diagnosis of end-stage HCM	1 (3%)
Echocardiographic findings at initial diagnosis of HCM	
LVDD, mm	46 ± 5
LVEF, %	61 ± 8
End-systolic left atrial diameter, mm	38 ± 8
Maximum LV wall thickness, mm	20 ± 4
Intraventricular septal thickness, mm	19 ± 4
Posterior wall thickness, mm	13 ± 3
Echocardiographic findings at diagnosis of end-stage HCM	
LVDD, mm	59 ± 6
LVEF, %	36 ± 10
End-systolic left atrial diameter, mm	44 ± 9
Intraventricular septal thickness, mm	11 ± 3
Posterior wall thickness, mm	10 ± 2
Subtype at initial diagnosis of HCM	
Asymmetric septal hypertrophy	25 (58%)
Concentric	11 (26%)
Apical	7 (16%)
Outflow tract or mid-cavity obstruction	0 (0%)
Therapy at diagnosis of end-stage HCM	
β–blocker	30 (70%)
ACE-I or ARB	35 (81%)
Spironolactone	26 (60%)
Amiodarone	21 (49%)
ICD	13 (30%)

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HCM, hypertrophic cardiomyopathy; ICD, implanted cardioverter defibrillator; LVDD, left ventricular diastolic dimension; LVEF, left ventricular ejection fraction; VF, ventricular fibrillation; VT, ventricular tachycardia.

Data are the mean ± SD or n (percentage).

in 30 (70%) of 43 patients (Fig. 1A). Among these 30 patients, 28 patients died of sudden death (n = 21) or progressive heart failure–related death (n = 7). As a result, the annual cardiovascular death rate, annual sudden death rate, and annual heart failure–related death rate was 13%, 10%, and 3%, respectively (Fig. 1B). Among the 21 patients who died suddenly, 1 patient had nonfatal cardiac arrest, 10 patients had sudden cardiac death, and 10 of the 11 patients receiving ICDs for primary prevention had appropriate ICD interventions. One of the 7 patients with heart failure–related death had undergone heart transplantation. After the diagnosis of end-stage HCM, 3 patients died of noncardiovascular death. The time interval between the diagnosis of end-stage HCM and the occurrence of sudden death or heart failure–related death was 3.6 ± 3.0 and 5.8 ± 3.7 years, respectively.

Clinical Characteristics According to Cardiovascular Mortality

To evaluate possible predictors of sudden death in patients with end-stage HCM, we divided the subjects into 3 clinical subgroups according to cardiovascular mortality, which were an alive group (n = 13), a heart failure death group (n = 7), and a sudden death group (n = 21) (Table 2). There was no significant difference in the incidence of familial HCM or a family history of sudden death among these 3 clinical subgroups. Also, there was no significant difference of nonsustained VT or the maximum LV wall thickness at the diagnosis of HCM among these subgroups. However, there was a significant difference in the incidence of syncope at the diagnosis of HCM among the three subgroups. In the present study, 9 of the 10 (90%) patients with syncope at the time of diagnosis of end-stage HCM died of sudden death during a mean follow-up period of 5 ± 3 years. Figure 2 shows the probability of sudden death for end-stage patients with or without syncope at the diagnosis of end-stage HCM. The presence of syncope was associated with a significantly increased risk of sudden death ($P < .001$). Investigation of the medications being used at the time of diagnosing end-stage HCM revealed no significant differences for angiotensin-converting enzyme inhibitors/angiotensin receptor blocker and spironolactone among the 3 clinical subgroups. However, use of β-blockers was significantly more common among surviving patients than patients with heart failure–related death (85% vs. 29%, $P = .012$). Also, the use of amiodarone by patients with sudden death was significantly more common than by surviving patients (67% vs. 31%, $P = .042$). On the other hand, there was no significant difference in the rate of ICD implantation among the 3 clinical subgroups. In 7 (54%) of the 13 patients with ICDs, use of the device was appropriate. The annual rate of ICD activation was 4.6%. At the diagnosis of end-stage HCM, echocardiographic parameters like LVDD and LVEF showed no significant differences among the 3 clinical subgroups (Table 2).

Predictors of Sudden Death in Patients with End-stage HCM

To evaluate possible predictors of sudden death for the HCM patients who progressed to end-stage HCM, we performed multivariate Cox proportional hazards analysis with stepwise selection of variables. In this multivariate model, established major primary prevention risk factors for sudden death were entered (positive family history, maximum LV wall thickness ≥30 mm at the initial diagnosis of HCM, nonsustained VT at the diagnosis of end-stage HCM, and unexplained syncope at the diagnosis of end-stage HCM). As a result, the presence of syncope at the diagnosis of end-stage disease was identified as an independent predictor of sudden death (hazard ratio = 6.15; 95% confidence interval, 2.40-15.75; $P < .001$).

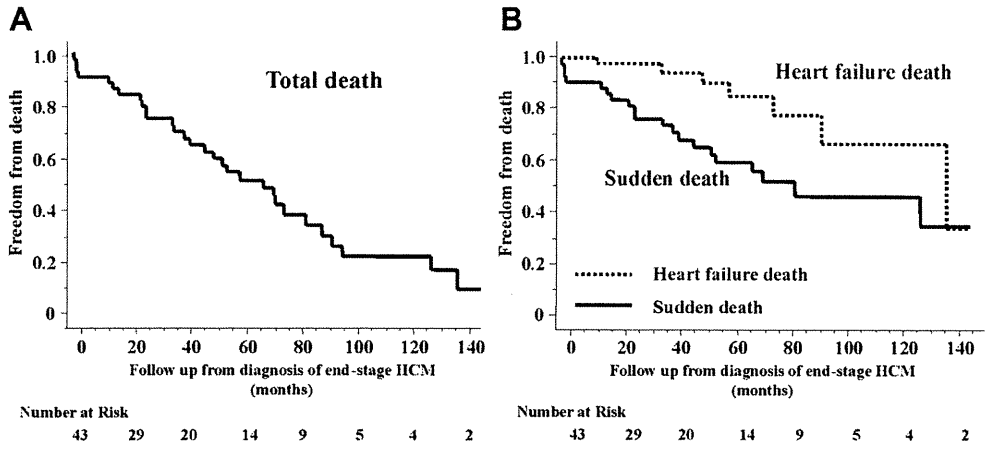

Fig. 1. Probability of cardiovascular mortality after the diagnosis of end-stage hypertrophic cardiomyopathy (HCM): (A) Total death, (B) Heart failure death and sudden death.

Discussion

This study demonstrated that 43 (8.8%) of 490 HCM patients progressed to end-stage disease during a mean follow-up period of 12 ± 7 years after the initial diagnosis of HCM, with the annual incidence of progression being 0.73%. The prevalence of cardiovascular mortality, especially sudden death, was also very high during a mean follow-up of 5 ± 3 years after the diagnosis of end-stage HCM. Furthermore, the presence of syncope at the time of diagnosing end-stage HCM diagnosis was an independent risk factor for sudden death among patients with end-stage HCM. Therefore, it is suggested that an aggressive therapeutic strategy for sudden death should be considered in patients with end-stage HCM, particularly those patients with syncope at the diagnosis of end-stage HCM.

Previous studies have shown that the prevalence of end-stage HCM was approximately 2.4 to 15%, with an annual incidence of 0.5 to 1.0%.[2–8] This study demonstrated that 43 (8.8%) of 490 HCM patients progressed to end-stage disease during a mean follow-up of 12 years, with the annual incidence being 0.73%. Regarding the long-term prognosis of patients with end-stage HCM, the present study showed that cardiovascular death occurred in 28 (65%) of 43 patients during a mean follow-up period of 5 ± 3 years after the diagnosis of end-stage disease and the annual cardiovascular mortality rate was 13%, suggesting a very poor long-term prognosis. Harris et al reported that 66% of end-stage HCM patients died of either heart failure or sudden cardiac death or needed an ICD or heart transplantation, and the annual adverse event rate was 11%.[6] The adverse event rate in our study was similar to previous data.[4–6] In

Table 2. Clinical Characteristics According to the Outcome

	Alive	Heart Failure Death	Sudden Death	
	(n = 13)	(n = 7)	(n = 21)	*P* Value
Age at initial diagnosis of HCM, y	43 ± 16	40 ± 19	45 ± 12	.384
Age at diagnosis of end-stage HCM, y	56 ± 11	54 ± 18	57 ± 11	.253
Male	10 (77%)	4 (57%)	18 (86%)	.284
Family history of HCM	4 (31%)	2 (29%)	10 (48%)	.512
Family history of sudden death	3 (23%)	2 (29%)	7 (33%)	.815
HCM-related morbidity at diagnosis of end-stage HCM				
Stroke	2 (15%)	4 (57%)	4 (19%)	.084
Heart failure	3 (23%)	2 (29%)	5 (24%)	.959
Syncope	1 (8%)	0 (0%)	9 (43%)	.017
Chronic atrial fibrillation at diagnosis of end-stage HCM	5 (38%)	4 (57%)	4 (19%)	.141
Nonsustained VT at diagnosis of end-stage HCM	7 (54%)	2 (29%)	16 (76%)	.067
LVDD at diagnosis of end-stage HCM, mm	57 ± 5	59 ± 3	60 ± 7	.221
LVEF at diagnosis of end-stage HCM, %	38 ± 9	35 ± 11	34 ± 10	.318
Therapy at diagnosis of end-stage HCM				
β–blocker	11 (85%)	2 (29%)	16 (76%)	.023
ACE-I or ARB	11 (85%)	5 (71%)	18 (86%)	.672
Spironolactone	8 (62%)	3 (43%)	15 (71%)	.391
Amiodarone	4 (31%)	2 (29%)	14 (67%)	.063
ICD	4 (31%)	1 (14%)	11 (52%)	.154

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HCM, hypertrophic cardiomyopathy; ICD, implanted cardioverter defibrillator; LVDD, left ventricular diastolic dimension; LVEF, left ventricular ejection fraction; VF, ventricular fibrillation; VT, ventricular tachycardia.
Data are the mean ± SD or n (percentage).

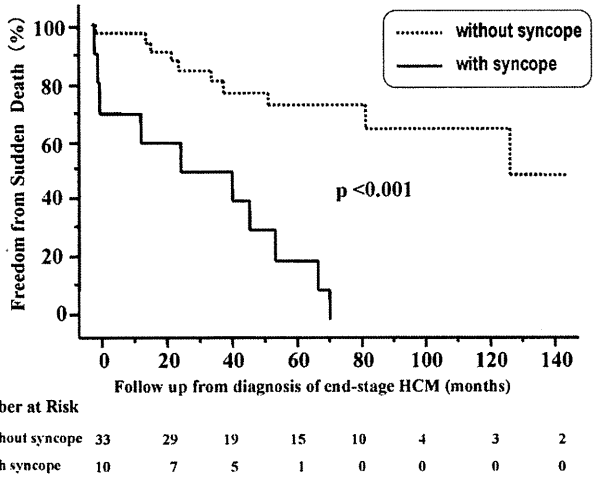

Fig. 2. Probability of sudden death in patients with end-stage hypertrophic cardiomyopathy (HCM) patients with or without syncope at the diagnosis of end-stage disease.

general, HCM is the most common cause of sudden death among young people, including competitive athletes, and sudden death is often the initial clinical manifestation of HCM.[1,8,17–20] Recently, Yacoub et al suggested that development of systolic dysfunction in HCM patients was associated with a high rate of heart failure–related mortality and sudden death.[9] Moreover, the onset of end-stage HCM represents a risk factor for sudden cardiac death and a potential indication for prophylactic ICD interventions.[9] However, it has been unclear whether sudden death was as common among HCM patients with end-stage disease as it is among HCM patients with preserved LV systolic function. In the present study, sudden death and heart failure–related death were observed in 78% and 22% of end-stage HCM patients, respectively, and the prevalence of sudden death was far higher than in previous reports.[4–6] The reason for this difference may be that the interval from diagnosis of end-stage HCM to heart transplantation was relatively short (less than 3 years) in previous reports, suggesting that early heart transplantation could prevent sudden death in patients with end-stage HCM from Western countries.[6] Another possible reason was that the use of β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and spironolactone showed obvious differences between previous reports and the present study. In particular, our data revealed higher administration rates of β-blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers among surviving patients compared with those who suffered from heart failure–related death. This is consistent with preliminary evidence that angiotensin-converting enzyme inhibitors may positively influence coronary microvascular dysfunction, which is associated with a higher incidence of end-stage HCM and a poor prognosis.[14] Moreover, the interval between the diagnosis of end-stage HCM diagnosis and sudden death or heart failure–related death was 3.6 ± 3.0 and 5.8 ± 3.7 years, respectively. This difference suggests that optimal medical therapy could prevent heart failure but not sudden death in patients who developed end-stage HCM. It has been reported that sudden death accounts for up to 50% of all deaths in patients with nonischemic dilated cardiomyopathy.[21] According to previous reports and our data, early detection of the end-stage phase could be regarded as another risk factor for sudden death in HCM patients, and prophylactic placement of an ICD in all end-stage HCM patients may be needed to prevent sudden death prior to heart transplantation.[6,17–19] However, further clinical research is needed to identify the optimal therapeutic strategy for end-stage HCM to prevent both heart failure death and sudden death in these patients.

Regarding risk factors for sudden death in end-stage HCM, our study showed that the presence of syncope at the diagnosis of end-stage disease was an independent predictor of sudden death by stepwise multivariate Cox proportional hazards analysis. Recently, it has been reported that syncope was a risk factor for sudden death in a large cohort of patients with HCM.[1,19,22,23] Therefore, end-stage HCM patients with syncope at the diagnosis of end-stage disease may have a substantially higher risk of sudden death than patients without syncope. However, further large-scale studies will be needed to confirm whether the presence of syncope is associated with sudden death in patients who progress to end-stage HCM.

The present study had several limitations. First, this study was retrospective nature and relatively small size. Second, the subjects of this investigation were limited to patients who were diagnosed as having HCM and followed-up at our hospital, which was the referral center, suggesting that center referral bias could influence our data on the clinical spectrum of end-stage HCM.[17,24] Third, in the present study, we defined sudden death as including appropriate ICD interventions. However, the definition of sudden death in patients with HCM remains unsettled.[25] Further clinical trials will be required to determine whether appropriate ICD intervention is a useful surrogate end point for sudden death in patients with HCM. Fourth, we could not evaluate the pathophysiological correlates of the progressive morphologic and functional changes identified in this study. Fifth, genetic analysis was not performed in our end-stage HCM patients, so we could not assess the correlations between genotype and phenotype.

In conclusion, this study demonstrated that patients with end-stage HCM have a high incidence of sudden death. Furthermore, end-stage HCM patients with syncope at the diagnosis of end-stage disease may have a substantially higher risk of sudden death than patients without syncope. Therefore, when HCM is evolving into the terminal phase, aggressive therapy for both heart failure death and sudden death should be considered. However, a further large-scale clinical study is needed to confirm whether the presence of syncope is associated with sudden death and to identify the optimal therapeutic strategy for HCM patients who progress to end-stage disease.

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Disclosures

None.

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Feasibility Evaluation of a Remote Monitoring System for Implantable Cardiac Devices in Japan

A Prospective Analysis

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SUMMARY

The number of implanted cardiac devices has been growing steadily over the last several years. Systems to monitor device data remotely have been introduced with the goal of reducing follow-up burden for both patients and physicians. Since the introduction of telemedicine depends greatly on the situations that are unique to each country, the acceptance of cardiac device remote monitoring in Japan was analyzed.

A total of 203 patients who had previously undergone cardiac device implantation were enrolled. The subjects were provided with a CareLink Monitor that performed interrogation and transmission of device data at home, and then the physicians reviewed the data via a website at one and 3 months after baseline visits. A total of 470 transmissions were made. Questionnaires were completed by subjects and physicians to evaluate acceptance, ease of use, and satisfaction with the system. More than 87% of the subjects felt the Monitor was easy to use and nearly all of the physicians were satisfied with the system. A majority of patients felt reassured by having their devices assessed from a remote location and preferred the decreased number of clinic visits that were possible when using the Monitor. The patients spent an average of 168.2 minutes per clinic visit, whereas follow-up time was reduced to 13.0 minutes by remote monitoring. Physician consultation time was reduced by 2.7 minutes.

The CareLink Network was well accepted by both the patients and physicians. Underlying issues did emerge, but once they are overcome, the system appears to have great potential to improve the quality of care given by healthcare providers. (Int Heart J 2011; 52: 39-43)

Key words: Device follow-up, Telemedicine, Feasibility study

The number of patients treated for cardiovascular diseases with implantable devices such as pacemakers and implantable cardioverter defibrillators (ICD) has been growing rapidly in recent years. Current devices are capable of continuous cardiac monitoring and storage of long-term trends in cardiac rhythms, episodes, and physical conditions. These data are often interrogated and assessed during in-office visits with the use of appropriate programmers. An ever growing demand for implantable device follow-up is stressing the capability of clinics to levels that are difficult to sustain. Therefore, a reduction of the burden by any means possible would have a significant positive impact on the quality of care provided by these physicians.

One solution may be the remote monitoring of implantable cardiac devices. The Medtronic CareLink Network (Medtronic, Inc., Minneapolis, MN, USA)[1)] utilizes an internet-based patient information management system. It is comprised of a patient monitor (Monitor), which interrogates and transmits device data via a standard analogue telephone connection, a secure server, in which the transmitted data are stored, and a clinician website, which offers the physician secure data access to patient data. Remote monitoring of ICD[1)] and cardiac resynchronization therapy with defibrillators (CRT-D)[2,3)] have been studied in the United States and Europe. Since the feasibility and acceptance of telemedicine depend heavily on the social, geographical, and economical situations of a country, in the present study we conducted assessments of the ease of use, satisfaction level, and acceptance of this system by both patients and physicians in Japan, and also discuss the impacts of the method on patient and physician time and burden.

METHODS

This study was a prospective, observational, nonrandomized clinical trial conducted at 5 centers in Japan. It was ap-

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proved by the Institutional Review Board or Medical Ethics Committee of each study site, and was carried out in accordance with the Ethical Guidelines for Clinical Studies (Ministry of Health, Labour and Welfare, July 30, 2003, amended on December 28, 2004).

Study population: The targeted number of subject enrollments per center was 35 to 50, with an expected minimum overall total of 200. Patients with previously implanted CareLink-compatible cardiac devices who had analogue telephone connections at home and were willing to sign the informed consent were enrolled. The study population was comprised of patients who had undergone implantation of a brady pacemaker, ICD, or CRT-D.

Subject follow-up: All subjects received conventional medical care in addition to guidance concerning the use of the Monitor for device interrogation and data transmission. The subjects had scheduled in-office study visits at baseline and at 6-months follow-up. They were also instructed to interrogate and transmit their device data using the Monitor at one and 3 months after the baseline visit. Subjects and physicians were asked to complete questionnaires with respect to satisfaction and ease of use of the CareLink system.

Successful data transmission: During the baseline visit, subjects were trained on how to setup the Monitor at home and perform data transmission. The Monitor was sent to their house directly from the manufacturer and the subjects were asked to complete initial setup on their own or with the assistance of caregivers. When a data transmission session was successfully completed without troubleshooting telephone calls, it was considered a "Successful Transmission". The success rates were calculated for 4 time points; scheduled transmissions at 1 month and 3 months after the baseline visit and unscheduled transmissions which were transmitted during the periods prior to (pre-one-month) or subsequent to (post-one-month) the first scheduled transmission at one month after the baseline visit.

Time and burden impact: Time and burden impact was compared between clinic visits and data transmissions for both the physicians and subjects. Clinic visit time was defined as the total time required to travel to and from the clinic, waiting to be seen at the clinic, and for the actual medical procedure. To assess the impact of remote monitoring on subjects and their caregivers, if applicable, questionnaires were administered to the subjects during baseline visits with main focuses on travel time, and amount of work time missed by the subjects and caregivers. The time required to perform scheduled and unscheduled data transmissions were also noted after each attempt.

Physicians were asked to document the time required to complete the follow-up visits for each subject. When transmitted data was received from the subjects, physicians evaluated the data via the internet and noted the time they spent to perform this procedure.

Statistical analysis: Categorical data are expressed as numbers and percentile. Continuous data are presented as the mean and standard deviation. Comparisons of continuous variables were made using Student's *t*-test or the Tukey-Kramer method. In order to compare multiple categorical data, Ryan's method was used. A P value less than 0.05 was considered significant. A control arm was not established due to the observational nature of the study.

RESULTS

Patient population: The first enrollment occurred on February 5, 2008, and the final follow-up was completed on March 19, 2009. The total number of subjects enrolled was 203. Twenty-two subjects withdrew from the study due to death (7), a subject leaving a study center (1), request for discontinuation by a subject (3), telephone line incompatibility (7), and subject lost to follow-up (4). Patient demographics are shown in Table I. Sixty-seven percent of the population was male, and mean age at baseline was 67.5 ± 13.6 years. More than half of the enrolled subjects were implanted with pacemakers, while 43.4% and 3.5% had ICD or CRT-D implantations, respectively. The most prominent cardiovascular condition was myocardial infarction with a prevalence of 18.2%. Sixty-six (32.5%) subjects had a history of atrial fibrillation. Other major conditions found

Table I. Patient Demographics

	(n = 203)
Gender: Male	136 (67.0%)
Age: Mean ± SD	67.5 ± 13.6
Device category	
IPG	108 (53.2%)
ICD	88 (43.4%)
CRT-D	7 (3.5%)
Cardiovascular history	
Cardiomyopathy	46 (22.7%)
Coronary artery disease	64 (31.5%)
Valve dysfunction	13 (6.4%)
Arrhythmia history	
Sick sinus syndrome	67 (33.0%)
Atrial arrhythmia	76 (37.4%)
Ventricular arrhythmia	110 (54.2%)
Conduction anomaly	66 (32.5%)

Table II. Proportion of Successful Transmissions

	Number of transmissions	Number of successful transmissions	% Success	95% CI
Pre-one-month unscheduled transmission	29	20	69.0	49.2-84.7
One-month scheduled transmission	190	132	69.5	62.4-75.9
Three-month scheduled transmission	183	169	92.3	87.5-95.8
Post-one-month unscheduled transmission	68	64	94.1	85.6-98.4
Total	470	385	81.9	78.1-85.3

CI indicates confidence interval.

Table III. Subject Satisfaction, Ease of Use, and Perspective

	Transmission			
	Unscheduled (Pre-one-month)	1 Month	3 Months	Unscheduled (Post-one-month)
Clarity of Monitor User Manual				
Very clear	6 (25%)	45 (26%)	54 (32%)	16 (32%)
Clear	13 (54%)	101 (59%)	108 (64%)	32 (64%)
Unclear	4 (17%)	24 (14%)	5 (3%)	1 (2%)
Very unclear	1 (4%)	0 (0%)	1 (1%)	1 (2%)
Ease of Monitor Set up				
Very easy	6 (25%)	55 (32%)	72 (43%)	18 (37%)
Easy	13 (54%)	91 (53%)	85 (51%)	28 (57%)
Difficult	4 (17%)	25 (15%)	8 (5%)	2 (4%)
Very difficult	1 (4%)	0 (0%)	2 (1%)	1 (2%)
Ease of Antenna Positioning				
Very easy	13 (54%)	81 (48%)	84 (50%)	27 (54%)
Easy	10 (42%)	82 (48%)	79 (47%)	19 (38%)
Difficult	1 (4%)	7 (4%)	3 (2%)	3 (6%)
Very difficult	0 (0%)	0 (0%)	2 (1%)	1 (2%)
Time Required for Transmission				
Very brief	0 (0%)	17 (10%)	25 (15%)	7 (14%)
Brief	17 (71%)	102 (61%)	124 (74%)	32 (65%)
Long	7 (29%)	41 (24%)	17 (10%)	8 (16%)
Very long	0 (0%)	8 (5%)	2 (1%)	2 (4%)
Overall Ease of Use of the Monitor				
Very easy	4 (17%)	51 (30%)	57 (34%)	15 (30%)
Easy	17 (71%)	97 (57%)	105 (63%)	32 (64%)
Difficult	2 (8%)	23 (13%)	5 (3%)	2 (4%)
Very difficult	1 (4%)	0 (0%)	1 (1%)	1 (2%)

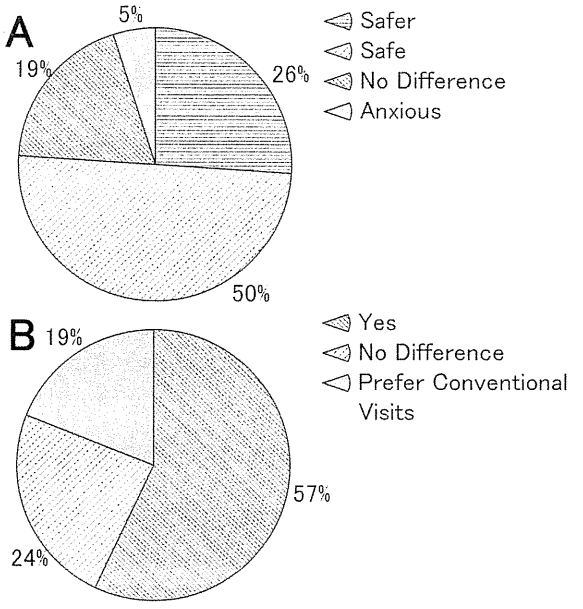

Figure. Patient perspective on the use of the remote monitoring system at the 6-month follow-up visit (n = 168). (**A**) How do you feel about physicians assessing the device data from a remote location? (**B**) Do you prefer the less frequent clinic visits when using the remote monitoring system?

among the population were hypertension in 83 (40.9%) and experience of cardiac syncope in 78 (38.4%).

Data transmission: Seven subjects discontinued the study due to telephone line incompatibility caused by their fiber-optic telephone systems and/or telephone service carriers. Internet-based telephone systems such as this fiber-optic network are gaining popularity and the number of analogue telephone lines is constantly decreasing in Japan, so this issue must be addressed in a timely manner. The success rate for data transmission using the Monitor is shown in Table II. A total of 470 transmissions were attempted during the study, of which 385 (81.9%) were classified as successful. Sixty-nine percent success was achieved for pre-one-month unscheduled and 1-month scheduled transmissions, whereas subsequent transmissions had a much higher success rate of over 92%. Multiple comparisons of each time point found that the differences in the success rates between pre-one-month unscheduled versus 1-month scheduled transmissions, and between 3-month scheduled versus post-one-month unscheduled transmissions were not significant. The difference in success rate between the first-time transmissions and those after was statistically significant ($P <$ 0.004). There were 97 instances of troubleshooting calls. The most frequent (33%) reason for a troubleshooting call was an incorrect configuration between the pulse and tone dialing. The Monitor is capable of handling either a pulse or tone dialing method when placing a phone call. The setting could be altered by flipping a switch on the device. The dialing method must match to what is being offered by the telephone service carriers, otherwise the device will not be able to place a call before initiating an internet connection. Communication environment related difficulties were seen in 20% and inquiries regarding the usage of the Monitor were posted from 21% of subjects. Twenty-four (25.1%) calls were considered to be irrelevant inquiries.

Subject satisfaction and ease of use: Feedback from the subjects on the use of the Monitor is summarized in Table III. A majority of the subjects found the user manual to be clearly written and understandable. Setting up the Monitor and positioning of the antenna on their implanted devices for interrogation was considered easy or very easy by more than 79% of subjects. Overall ease of use was also favorably perceived.

Even though a large proportion of subjects provided positive feedback, somewhat mixed results were seen with the time required for transmission. This was considered to be caused by the subjective nature of the inquiry. One person may feel 10 minutes is very long, while another may feel it is short.

The results indicated that the subjects felt more confident with the Monitor after using it the first time since shorter transmission times and increases in affirmative feedback were seen with later transmissions. This suggests the importance of training at the clinic before initiating the use of this remote monitoring system.

Do you like remote monitoring?: During their final study visit, ie, 6-month follow-up visit, the subjects were asked to evaluate their experience with remote monitoring. A majority (76%) of the subjects felt it was safe or safer than before to have their device data monitored remotely by the physicians (Figure). In contrast, 5% felt some anxiety. Certain patients may need to have all consultations in person with their physician. An appropriate method for selection of suitable patients will be needed when remote monitoring becomes the standard of care.

More than half of the subjects replied that they preferred the lower number of clinic visits associated with the use of a remote monitoring system.

Physician satisfaction and ease of use: Feedback from the physicians regarding the quality of the website is summarized in Table IV. All the responses were positive, with the exception of a single doctor for the one-month transmission. Physicians were confident about the accessibility and search capability of the secure website. Work flow applied to unscheduled transmissions at individual and organizational levels has yet to be standardized, and it may have had some influence on the somewhat lower ratings seen for unscheduled transmissions. The device data collected through the website were comparable to the data obtained with direct device interrogation at the clinic, and they were deemed satisfactory to all physicians, except on one occasion.

Comparison of time burden impact: The time required for the baseline clinic visits and each data transmission for the subjects are compared in Table V. Direct comparison of the actual time required for data transmission and clinic visits revealed that the time necessary for data transmission was significantly shorter than for a clinic visit.

A majority of the subjects (54%) used cars as the mode of transportation to the clinic. Assistance by a caregiver was needed by 58% and 45% of the study population when going to their clinic visits at baseline and 6-month follow-up, respectively. When making these visits, more than one quarter of the subjects and one third of the persons accompanying the subject missed work that day (data not shown).

Physicians spent a mean of 9.05 ± 4.84 minutes and 6.35 ± 5.10 minutes for scheduled in-clinic device follow-ups and review of transmitted data, respectively. The difference of 2.70 minutes was statistically significant ($P < 0.001$). Further comparison of individual time points revealed that unscheduled in-clinic visits took a significantly longer period of time, whereas the difference between unscheduled transmissions and regular in-clinic visits was not significant.

Table IV. Physician Satisfaction and Ease of Use

	Transmission		
	1 Month	3 Months	Unscheduled
Ease of Access to the Website			
Very Easy	122 (70%)	126 (70%)	37 (38%)
Easy	51 (29%)	54 (30%)	60 (62%)
Difficult	1 (1%)	0 (0%)	0 (0%)
Very Difficult	0 (0%)	0 (0%)	0 (0%)
Ease of Search through the Website			
Very Easy	113 (65%)	117 (65%)	32 (33%)
Easy	60 (34%)	63 (35%)	65 (67%)
Difficult	1 (1%)	0 (0%)	0 (0%)
Very Difficult	0 (0%)	0 (0%)	0 (0%)
Data Comparability against Conventional Follow-up			
Strongly Agree	71 (41%)	50 (28%)	9 (9%)
Agree	102 (59%)	130 (72%)	88 (91%)
Disagree	1 (1%)	0 (0%)	0 (0%)
Strongly Disagree	0 (0%)	0 (0%)	0 (0%)

Discussion

It is well accepted that telemedicine may have the potential to bring about major improvements in healthcare systems, but in reality, it is reported that 75% of telemedicine initiatives failed during the operational phase.[4] Tanriverdi and Iacono (1999) introduced a theory stating that knowledge barriers inhibit the diffusion of telemedicine. Those barriers were based on technical, behavioral, economical, and organizational aspects.[5] Broens, *et al* (2007) further expanded this theory by adding a policy and legislation standpoint.[6] All of these barriers must be lowered in order to achieve successful deployment and long-term implementation of remote monitoring systems in daily medical practice.

In the present study, technical difficulties unique to Japan, such as telephone line issues, were encountered. Some of these concerns were solved during the course of the study, but since 30% of the subjects had difficulty with their first transmissions, improvements in training and support are needed. From a behavioral point of view, it is clear that the CareLink Network was well accepted by both patients and physicians. To achieve long-term success with the system, its benefits must be promoted based on the medical evidence obtained thus far.

It is evident that patients are sure to benefit from the time, cost, and labor savings. However, for physicians and clinics, only a slight reduction in follow-up time was demonstrated. This study may have been a success because it was funded research and the follow-up duration was short. Further discussion is necessary to assess the correlation between the reduction of labor and economical impact for the physicians. Each organization must set up their own standard operation procedure in order to run the system smoothly. Current forms of legislation and policy are not best suited for new telemedicine technologies. If these could be addressed and the procedures

Table V. Time Burden Impact

	Clinic Visit			Transmission		
(Minutes)	Baseline	6 Months	Unscheduled	1 Month	3 Months	Unscheduled
Subject	(n = 196)	-	-	(n = 169)	(n = 166)	(n = 74)
Mean	168.2 ± 95.7	-	-	14.7 ± 23.7	9.7 ± 5.6	16.3 ± 26.2
Median	150	-	-	10.0	10.0	10.0
Min-Max	10.0-510.0	-	-	2.0-270.0	3.0-40.0	1.0-180.0
Physician	(n = 153)	(n = 130)	(n = 13)	(n = 173)	(n = 180)	(n = 95)
Mean ± SD	9.4 ± 5.2	8.7 ± 4.3	14.8 ± 6.9	6.6 ± 4.7	6.2 ± 5.5	7.9 ± 6.1
Median	8.0	7.0	15.0	5.0	5.0	9.0
Min-Max	4.0-20.0	5.0-20.0	5.0-30.0	1.0-20.0	1.0-30.0	1.0-30.0

standardized, the feasibility of such systems would greatly improve.

The pros and cons of telemedicine are currently being discussed.[7,8] Without question, a face-to-face consultation with a physician can never be totally replaced by telemedicine. However, the dramatic increase in the elderly population will have a great impact on device clinics due to the ever-growing demand for cardiac devices. Actions must be taken in order to decrease the burden on such physicians to enhance the overall quality of care. Reducing follow-up time by the use of remote monitoring may be a promising solution.

Medical economic evaluation using the CareLink Network has been performed in Europe.[9] Although the results can not be directly applied to the situation in Japan, it is possible to perhaps predict the potential influence the system may have. The objective of the current study was not to evaluate symptom oriented data transmission from the patients. In order to collect more evidence regarding the clinical efficiency of the CareLink Network, randomized trials to evaluate disease management and patient outcomes as well as medical economical endpoints are needed.

Limitations: The design of the present study was nonrandomized and uncontrolled. Some of the data collected was subjective in nature, and some data were missing since a proportion of the questionnaires could not be retrieved from the subjects and physicians.

Conclusions: The present study has demonstrated that remote monitoring of implantable cardiac devices utilizing the CareLink Network System was well accepted by both a representative population of patients and physicians in Japan. Such a system has the potential to improve clinical efficiency and the way cardiac disease is managed. Certainly there are hurdles that must be cleared before widespread employment of the system, but once these obstacles are overcome, the system will most likely have an enormous impact on how care is delivered to patients. Physicians may also benefit from the reduction in time needed for follow-up.

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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]

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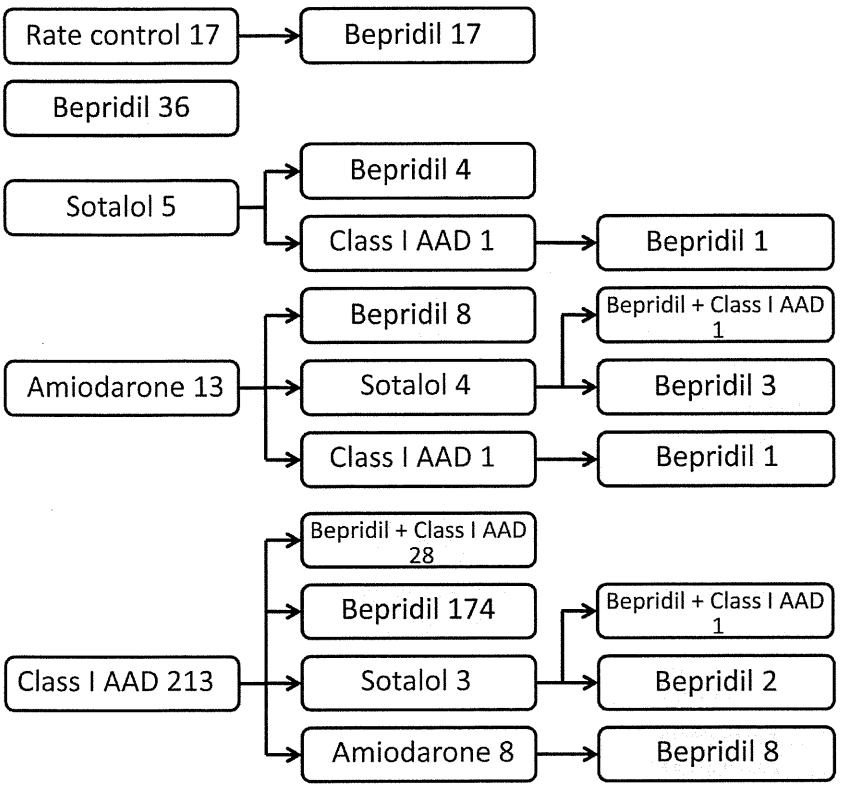

Figure 1. History of antiarrhythmic drug (AAD) use in paroxysmal or persistent atrial fibrillation patients receiving bepridil.

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 procedures. 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.

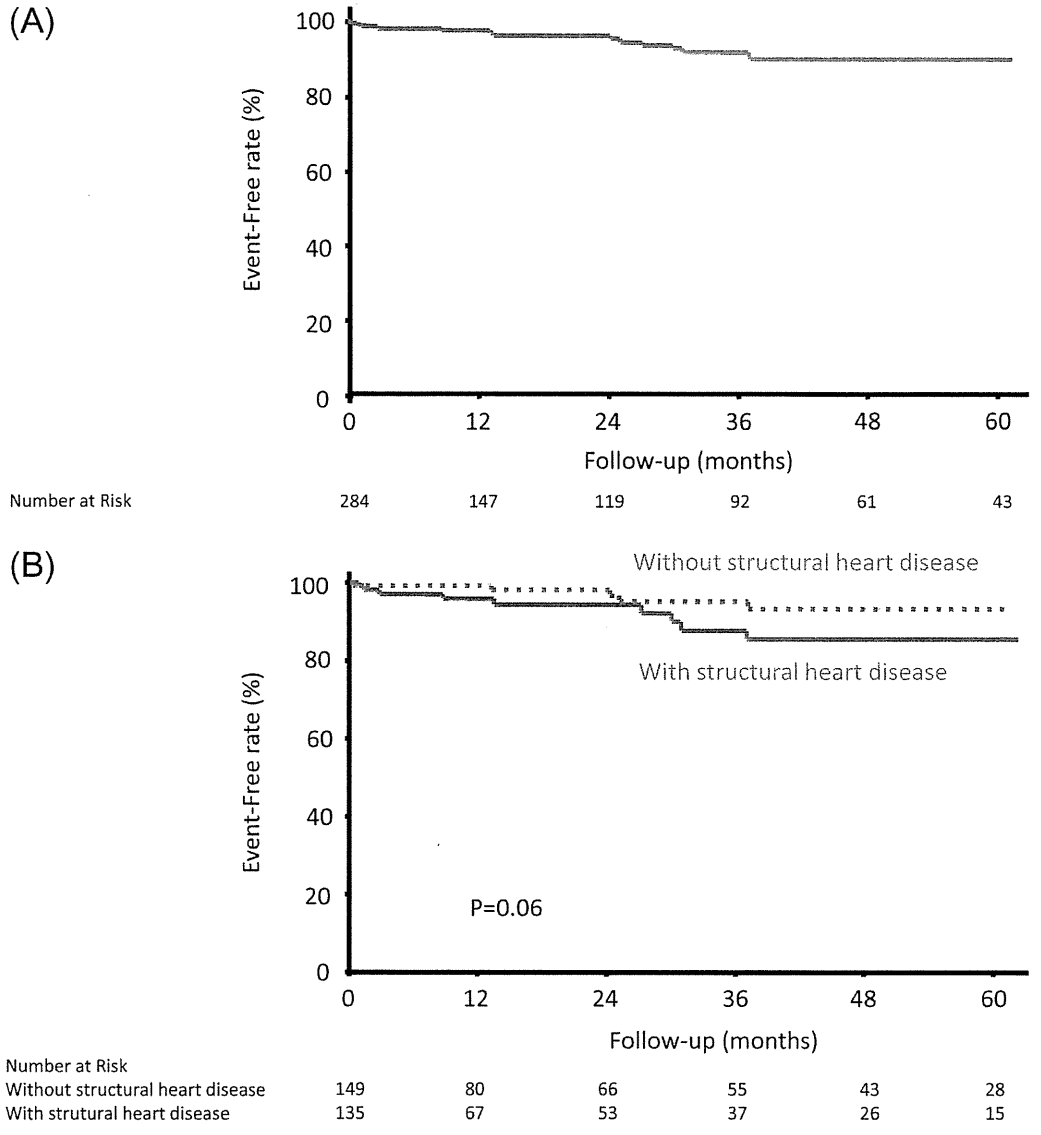

Figure 2. (A) Kaplan-Meier curve for the primary endpoint (composite cardiovascular events) in paroxysmal or persistent atrial fibrillation patients receiving bepridil. (B) Kaplan-Meier curve for the primary endpoint in patients with and without structural heart disease.

Side Effects

We observed bepridil-related cardiac adverse events, including sudden arrhythmic death, ventricular tachyarrhythmia (including Tdp), excessive QTc prolongation (>0.50 s), excessive bradycardia requiring the discontinuation of bepridil and/or additional therapy. Extracardiac adverse events, such as gastrointestinal symptoms and liver dysfunction (alanine aminotransferase ≥3×normal and/or alkaline phosphatase >normal), were also observed.

Statistical Analysis

Summary data are presented either as mean±SD or number of patients. Categorical variables were subjected to chi-square analysis. Time to first occurrence of events was analyzed using the Kaplan-Meier method with the log-rank test. $P<0.05$ was considered significant. Data analyses were performed with SPSS statistical software (version 11.01, SPSS Inc, Chicago, IL, USA).

Results

Patients' Characteristics

The patients' baseline characteristics are shown in Table 1. The mean age when bepridil was started was 59±13 years, and 25% of the patients treated were women. A total of 21 patients (7%) had persistent AF; 135 patients (48%) had structural heart diseases; 63 (22%) had a history of congestive heart failure; 80 (28%) had hypertension; 39 (14%) had diabetes. Regarding concomitant medications at baseline, 126 patients (44%) had taken angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, 143 patients (50%) had taken β-blockers, and 38 patients (13%) had taken

Table 2. Death and Cardiovascular Events in the Patients With AF

Cardiovascular death	
Sudden death	1
Heart failure	5
Cerebral infraction	1
Dissection of aorta	1
Non-cardiovascular death	6
Non-fatal myocardial infarction	1
Hospitalization for unstable angina	2
Hospitalization for heart failure	1
Non-fatal cerebral infarction	5
Non-fatal cerebral hemorrhage	2
Torsade de pointes	2

Values are n. AF, atrial fibrillation.

a statin. The proportion of patients with a $CHADS_2$ score of 0, 1 or ≥2 was 44%, 31% and 25%, respectively. 152 patients (54%) used warfarin, and 108 (38%) used aspirin. We lost 8 patients to follow-up; the remaining 276 patients (97%) were followed completely. Bepridil was discontinued because of ineffective prevention of AF (86 patients), progression to permanent AF (30 patients), side effects (17 patients) or the patient's own decision (1 patient). The median follow-up period was 17 months (range 4–157 months).

Endpoints

The Kaplan-Meier curve for the primary endpoint is shown in Figure 2. Each primary endpoint is shown in Table 2. A primary endpoint was obtained for 21 (7%) of the 284 patients. The cumulative rate for the time to first cardiovascular event at 1, 3, and 5 years was 2.4%, 8.1%, and 10.1%, respectively. A trend toward increased cardiovascular events was observed

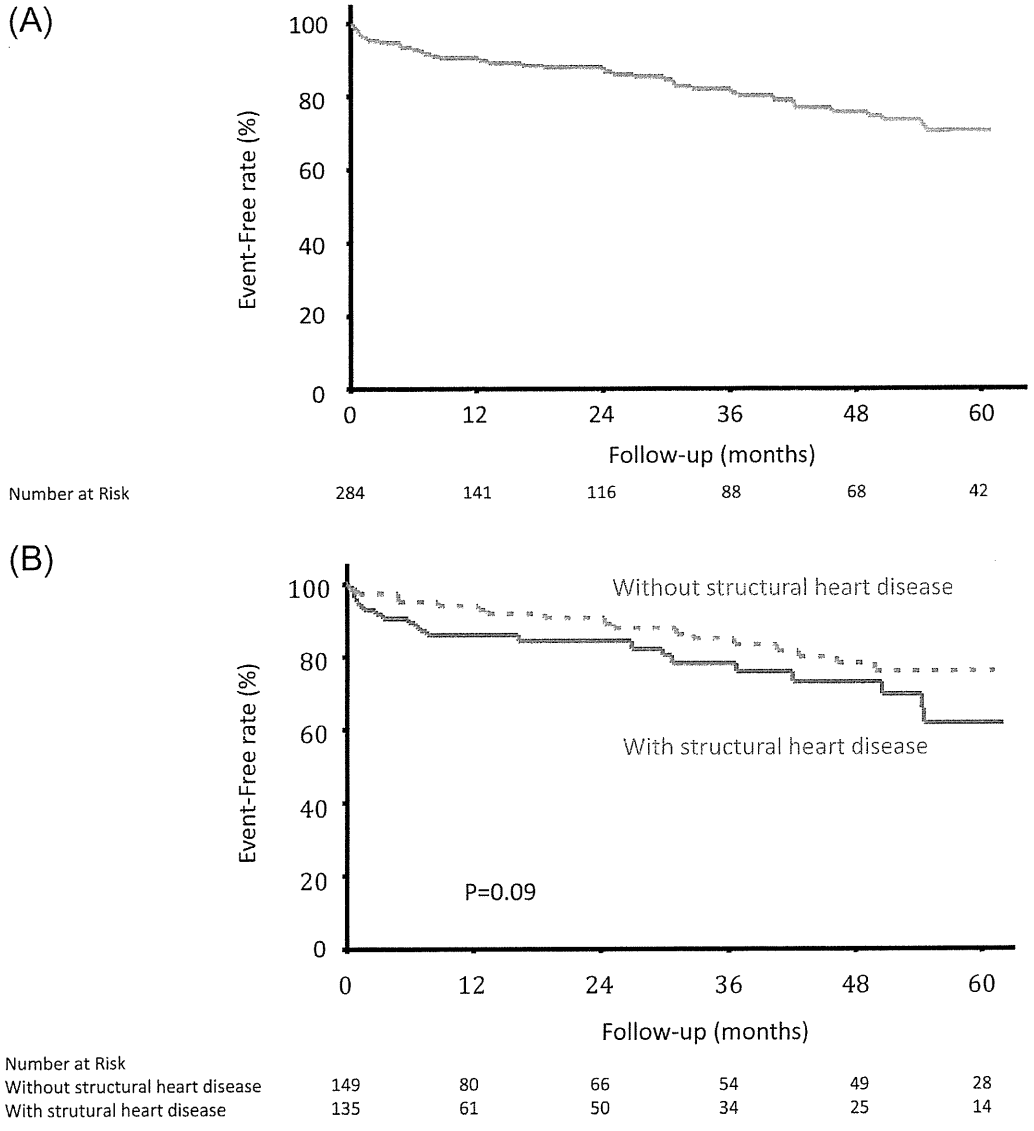

Figure 3. (A) Kaplan-Meier curve for the main secondary outcome (composite of mortality, symptomatic cerebral infarction, systemic embolism, major bleeding and hospitalization for heart failure) in paroxysmal or persistent atrial fibrillation patients receiving bepridil. (B) Kaplan-Meier curve for the main secondary endpoint in patients with and without structural heart disease.

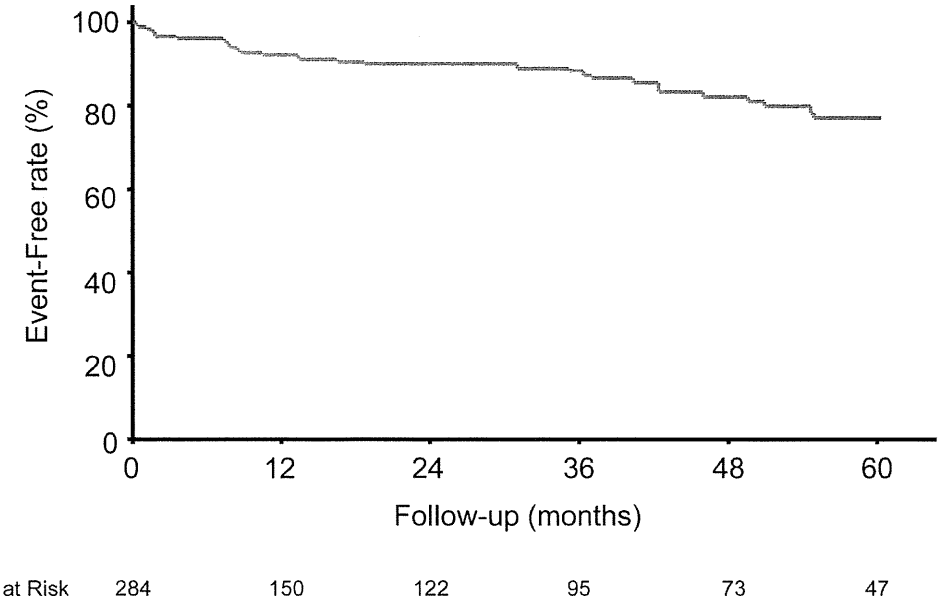

Figure 4. Kaplan-Meier curve for the progression to permanent atrial fibrillation in paroxysmal or persistent atrial fibrillation patients receiving bepridil.

in patients with structural heart disease compared with those without. The Kaplan-Meier curve for the main secondary outcome is shown in Figure 3. The cumulative rate for the main secondary endpoint at 1, 3, and 5 years was 9.7%, 18.2%, and 29.6%, respectively. A trend toward higher rates for the main secondary endpoint was observed in patients with structural heart disease compared with those without. The causes of death were sudden death (1 patient), heart failure (5 patients), dissection of aorta (1 patient) and non-cardiac causes (7 patients). Permanent AF was the diagnosis in 39 patients during bepridil therapy. The cumulative rate for the time to permanent AF diagnosis at 1, 3, and 5 years during bepridil therapy was 8.3%, 12.1%, and 23.5%, respectively (Figure 4).

Adverse Events

The numbers of patients who experienced adverse events according to their maintenance dose of bepridil are shown in Table 3. Regarding serious adverse events, sudden death occurred in 1 patient who had a prior MI (200 mg daily), and Tdp occurred in 2 patients without structural heart disease (both 200 mg daily). The rate of QTc prolongation (>0.50 s) was highest (11%) in patients taking 200 mg bepridil. A total of 17 patients (6%) discontinued bepridil therapy due to its side effects, which included the following: Tdp (2 patients), QT prolongation (3 patients), sinus bradycardia (1 patient), and non-cardiac causes such as gastrointestinal symptoms (4 patients), liver dysfunction (4 patients) and neurological symptoms (3 patients).

Blood Concentration

The distribution of plasma bepridil concentrations according to the maintenance dose (77 patients, 439 points) is shown in Figure 5. With dosages of ≤100 mg daily, a dose-dependent effect was observed. However, a high variation in plasma concentration was found, and a dose-dependent effect was not always observed with dosages ≥100 mg daily. Excessive QTc prolongation (>0.50 s) was found in plasma concentrations >800 ng/ml.

Table 3. Daily Dose of Bepridil and Adverse Events in the Patients With AF

	<100 mg	100 mg	150 mg	200 mg
n	22	112	106	44
Torsade de pointes	0	0	0	2
QTc prolongation (>0.50 s)	0	7	9	5
Bradycardia	1	0	0	0
Gastrointestinal symptoms	0	1	2	1
Liver dysfunction	0	0	3	1
Neurological symptoms	0	2	0	1

Values are n. AF, atrial fibrillation.

Discussion

Our study revealed the following: (1) a probability of cardiovascular events of 10.1% at 5 years in AF patients receiving bepridil; (2) a total of 75.7% of patients receiving bepridil had paroxysmal or persistent AF that was refractory to class I antiarrhythmic drugs; (3) a probability of progression to permanent AF of 23.5% at 5 years in paroxysmal or persistent AF patients receiving bepridil; (4) adverse events, especially Tdp, seemed to occur in a dose-dependent manner; (5) high variation in plasma concentrations even among patients taking the same dose of bepridil, and excessive QTc prolongation occurred mostly at concentrations >800 ng/ml.

In our study, we evaluated clinical outcome (AF-related, complicated heart disease-related and bepridil-related) as the primary endpoint and general outcome in AF patients (for comparison with the previous AF outcome study in Japan) as the main secondary endpoint. On average, our subjects were 10 years younger than the subjects in previous AF mortality

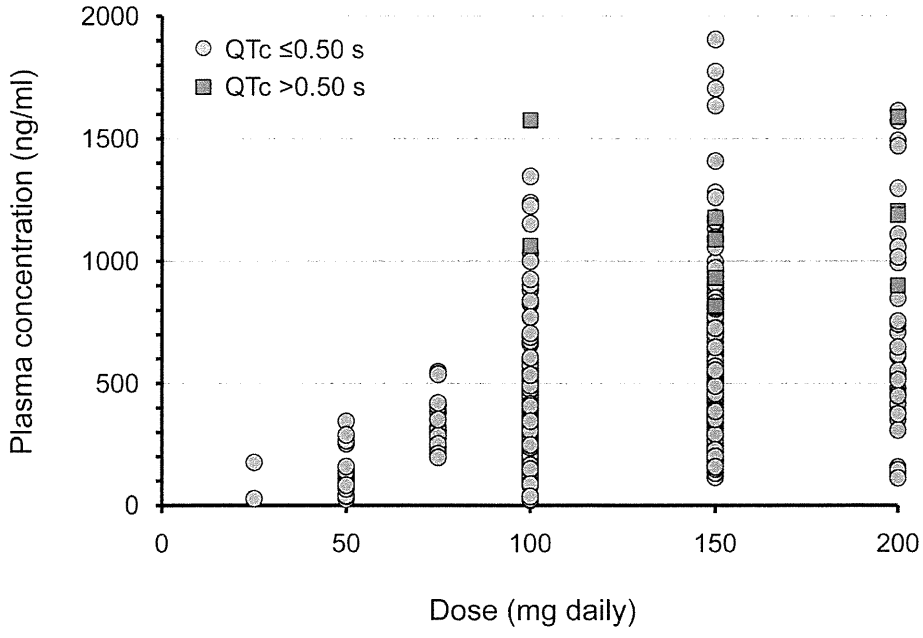

Figure 5. Dose and plasma concentration in 77 paroxysmal or persistent atrial fibrillation patients receiving bepridil (439 points).

studies, so the mortality and cardiovascular event rates were low.[10,11] However, the overall rate of the main secondary outcome, which was the hard endpoint in the J-RHYTHM study, was higher than in the J-RHYTHM study, in which the subjects were older (mean age: 65 years).[13] In particular, both the incidence of death due to worsening heart failure and of non-cardiac death was high in our study. Compared to subjects in the J-RHYTHM study, our subjects had a similar distribution of $CHADS_2$ scores, but a higher proportion of patients in our study had structural heart disease or a history of congestive heart failure. A trend toward a higher rate of cardiovascular events in patients with structural heart disease compared to patients without structural heart disease was observed. Nevertheless, because the proportion of warfarin use among our patients was similar to that in the J-RHYTHM study, the incidence of stroke was identical (our study: 2.1%; J-RHYTHM study: 2.1%[13]). Although the clinical backgrounds of the patients contributed to the outcomes, bepridil may not be helpful in improving the outcomes of AF patients with structural heart disease.

The Canadian Registry of Atrial Fibrillation study consisted of 757 patients with paroxysmal AF (mean age: 61 years; ≈40% with structural heart disease). This study showed that the probability of progression to permanent AF was 8.6% and 24.7% at 1 and 5 years, respectively.[31] Moreover, another study with a small sample number reported that among patients with drug-intolerant or drug-refractory paroxysmal AF on long-term antiarrhythmic drug therapy, the probability of progression to permanent AF was more than 30% at 5 years.[32] Factors such as age and structural or substrate abnormalities contribute to the progression to a permanent form of AF.[31,33] The rate of progression to permanent AF was not as high among our subjects (mean age: 59 years; 48% with structural heart disease) as in previous studies, even though our subjects were mostly AF patients who did not respond to class I antiarrhythmic drugs. Bepridil is an antiarrhythmic drug with multiple therapeutic actions,[15,16] and it has been found to be effective in converting AF to sinus rhythm and maintaining sinus rhythm in persistent AF or AF that is refractory to class I antiarrhythmic drugs.[17–24]

However, the safety of bepridil is a major problem, especially with respect to Tdp associated with QT prolongation.[15–25,34] In our study, sudden death and Tdp occurred in patients who took 200 mg daily. Moreover, 17 patients (6%) discontinued bepridil therapy due to its side effects, including QT prolongation, which seem to occur in a dose-dependent manner. Hypokalemia, bradycardia, heart failure, LV hypertrophy and high drug concentrations are recognized as risk factors for Tdp in the presence of a culprit drug.[35] In practice, as long as bepridil is used to manage AF, physicians must carefully monitor these factors, and bepridil should be avoided in AF patients with heart failure or LV hypertrophy.

We also monitored the blood concentration of bepridil, starting in May 2007. Bepridil has complex pharmacokinetic properties: low systemic bioavailability (approximately 60%), a large volume of distribution (8 L/kg), and a long elimination half-life (1–2 days) with a single oral dose and even longer at steady state.[26,27] Therefore, large interindividual differences in blood concentrations were observed, even among patients taking the same dose. Sugi et al reported that the bepridil blood concentration was 270±140 ng/ml in patients receiving 100 mg daily, 530±520 ng/ml in patients receiving 150 mg daily and 680±360 ng/ml in patients receiving 200 mg daily. Additionally, the proportion of patients whose AF was prevented by taking bepridil (vs. those who continued to experience AF while taking bepridil) was highest among patients receiving 200 mg daily with blood concentrations >600 ng/ml.[36] In contrast, Kurita et al reported that most of the patients who developed Tdp during bepridil therapy had taken 200 mg daily and had blood concentrations >500 ng/ml.[37] This demonstrates that there is considerable overlap between the effective dose/concentration and toxicity with bepridil therapy. In our results,

excessive QTc prolongation occurred in patients with plasma bepridil concentrations >800 ng/ml, and blood concentrations of at least 1,000 ng/ml might be a risk factor for developing Tdp. After we began monitoring blood concentrations, the mean maintenance dose of bepridil was decreased from 141±46 mg daily (February 1988 to April 2007) to 126±44 mg daily (May 2007 to August 2010). No Tdp occurred from June 2007 onward.

Study Limitations

First, this study was a retrospective observational study conducted in a single center, so treatment bias existed. We could not evaluate the relationship between AF recurrence and outcome. It is difficult to obtain the exact time to first recurrence or the frequency of AF recurrence from a patient's symptoms and routine ECGs in clinical practice. Second, the clinical characteristics of the subjects varied, and the number of subjects was small. Therefore, subgroup analysis was not feasible.

Conclusions

Bepridil is mostly used as a second-line therapy for AF patients who are refractory to class I or class III antiarrhythmic drugs. However, bepridil might not improve the clinical outcomes in these AF patients, especially those with structural heart disease. Moreover, its severe adverse events, including QT prolongation and Tdp, occur in a dose- and concentration-dependent manner. Monitoring the blood bepridil concentration and low-dose treatment regimens may help decrease adverse events.

Acknowledgments

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Disclosure

Competing interests: None declared.

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