integrity of the lead. The recovery and wound healing following this procedure takes a few days. A replacement of the ICD body only does not seem to affect the occurrence of either appropriate or inappropriate ICD therapies. However, any substantial evidence for this generally accepted notion remains scant. To the best of our knowledge, this is the first report to demonstrate that there was no difference in the incidence of ICD therapies before and after ICD replacements. Therefore, the replacement of the ICD body did not have an adverse effect on the ICD patients. In contrast, we found a case in which the replacement of the ICD affected the inappropriate ICD therapy. The cause of the inappropriate therapy was a change in the therapy algorithm. Essentially, an ICD using a similar algorithm as the previous one, and made by the same manufacturer, should be implanted in order to avoid any unnecessary inappropriate ICD therapies. Inappropriate therapies are often caused by supraventricular tachycardias including sinus tachycardia, and those arrhythmias occur more often during the patient's routine daily life than during their hospitalization. During hospitalization, patients often keep quiet and supraventricular tachycardias including sinus tachycardia are unlikely to happen. After the replacement of an ICD, it will take several days before the patient resumes their daily routine life. Therefore, we concluded that patients should refrain from driving for at least 1 week or so, including an extra few days before resuming their daily life.

In our study, the overall incidence of patients who experienced an ICD therapy was 12.2% and this number was lower than that in previous studies.[20,21] This might be because our population included more Brugada syndrome patients and fewer patients with coronary artery disease. In fact, 22 asymptomatic Brugada patients were included in our study. This group of patients, although not statistically significant, showed better prognosis than the others (Log rank P=0.18). During the follow-up period of 2.15±1.20 years, only 2 out of those 22 patients had ICD therapy. At this level of incidence, 12.2% is much lower than the threshold limit of 22%, which is defined in the consensus statement published by the ESC. Actually, in most patients, it is considered safe to give them permission to drive. However, our investigation showed that there was a high risk for those patients who have had recent ICD therapy. **Table 6** demonstrates that stricter regulations would result in the lower incidence of ICD therapy. However, even in patients with a 3 month incident-free period before the replacement, the annual incidence of ICD therapy after the replacement was 11.3%. This probability is still lower than acceptable level of 22%, as presented above.[11]

As shown in **Figure 1**, the number of ICD therapies that occurred after device replacement in those patients legally prohibited from driving was high. Although the overall incidence of ICD therapy was reasonably low, the result might be due to the large number of low-risk patients such as asymptomatic Brugada patients. If we expand driving permission drastically, the incidence of cardiac events during driving could increase. Considering this fact, we need to carefully monitor high-risk patients with recent ICD therapies in order to prevent serious car accidents.

Defibrillation Threshold Test (DFT)

We performed a DFT in 115 out of 128 (89%) of patients. Some reports have been published with respect to the risk of DFT.[22,23] Ventricular fibrillation and shocks during DFT could cause myocardial depression and might cause the subsequent VT/VF induction and result in frequent ICD discharge. However, the incidence of clinically significant myocardial depression and ventricular fibrillation after the DFT is limited and our data showed no significant effect on the rate of ICD therapies after the ICD replacement. We conclude that the DFT, at the time of ICD replacement, cannot affect the subsequent ICD discharge.

Study Limitations

This study had some limitations. First, one-third of our cohort consisted of Brugada syndrome patients, partly because the prevalence of Brugada syndrome is estimated to be high in Asian countries.[24] These patients often experience life-threatening arrhythmia or syncope during the resting state and sleep, and seldom develop life-threatening arrhythmias during driving. Second, this study was a retrospective cohort study. Third, a complete in-depth analysis of the distribution of the clinical variables in relation to the different manufacturers or different device models was not performed. And finally in this study, we did not separately analyze the patients who received appropriate and inappropriate therapies.[25]

Conclusion

There was no evidence that ICD replacements increased the incidence of ICD therapies, if the replacements ICD were from the same manufacturer. Accordingly, these data do not support the unnecessary long restrictions on driving after an ICD replacement, and low risk patients should be allowed to resume driving as early as possible. In our opinion, we conclude that in patients who are allowed to drive before the ICD replacement within 1 week or so, including a few extra days to resume their usual life, this time frame should be adequate for the safety review. However, considering a case whereby ICD therapy was given after an ICD replacement, using one from another manufacturer, this conclusion should only apply to those patients receiving only the replacement of the generator and not a change in the programming of it.

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Disclosures

This manuscript represents original work that has not been published and is not being considered for publication elsewhere in whole or in part in any language except as an abstract. All co-authors have read and approved the submission of the manuscript. There are no financial or other relations that could lead to a conflict of interest (Conflict of Interest: none declared).

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ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Predictors of Electrical Storm in Patients With Idiopathic Dilated Cardiomyopathy

– How to Stratify the Risk of Electrical Storm –

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Background: Electrical storm (ES) is a serious problem in patients with an implantable cardioverter defibrillator (ICD). However, insufficient reports have indicated the predictors of ES in ICD patients with idiopathic dilated cardiomyopathy (DCM). The purpose of this study was to clarify the predictors of ES for risk stratification in DCM patients with an ICD.

Methods and Results: Of 446 ICD patients, 53 DCM patients were included in this study. During a mean follow-up of 55±36 months, ES (≥3 times appropriate ICD therapy within 24 h) occurred in 18/53 (34%) patients. According to multivariate Cox proportional hazard regression analysis, a duration of the terminal low amplitude signals of <40 μV (LAS40) (HR 1.4/10 ms increase, 95% confidence interval (CI) 1.1–2.1; P=0.0049) or root mean square voltage of the last 40 ms of the QRS complex (RMS40) (HR 0.88/1 μV, 95%CI 0.77–0.96; P=0.001) on the signal averaged electrocardiogram, and a history of atrial fibrillation (AF) before ICD implantation (HR 2.3, 95%CI 1.2–5.0; P=0.013) were independently associated with an increased risk of ES.

Conclusions: Our data indicated that a longer LAS40, lower RMS40 and history of AF before ICD implantation could strongly predict ES, and the combination of those parameters could effectively stratify the risk of ES in DCM patients. (*Circ J* 2010; **74:** 1822–1829)

Key Words: Dilated cardiomyopathy; Electrical storm; Implantable cardioverter defibrillator; Signal averaged electrocardiogram; Ventricular tachyarrhythmias

Implantable cardioverter defibrillators (ICDs) have a high success rate in terminating life-threatening ventricular arrhythmias, including ventricular tachycardia (VT) or ventricular fibrillation (VF), and have become an established therapeutic option for reducing the risk of sudden cardiac death.[1,2] In primary prevention, 21% of patients receive the benefit of ICD with an appropriate therapy within 5 years as shown in the SCD-HeFT trial,[3] whereas in secondary prevention, this is the case for as many as 69–85% patients within 3 years as shown in the AVID trial.[4] However, some patients receive multiple shock therapies in a short period, which is referred to as an electrical storm (ES).[5] Although the incidence of ES is only 4% when ICDs are implanted for primary prevention according to the MADIT II trial,[6] and 10–28% over a 1- to 3-year follow-up period for secondary prevention.[1,7–9]

Since there has been an increase in ICD indications, ES has become an important issue because of all the clinical, psychological and economical consequences involved. Although several studies have reported the incidence, predictive factors and clinical prognosis of ES in patients with coronary artery disease, sufficient data does not exist regarding idiopathic dilated cardiomyopathy (DCM). The purpose of this study was to clarify the predictors and prevalence of ES for risk stratification in DCM patients with an ICD.

Methods

Study Population

Among our cohort of 446 ICD patients, 53 consecutive DCM patients (41 men and 12 women, mean age 55±15 years) who received an ICD between 1990 and 2004 at the National

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Cardiovascular Center, Suita, Japan, were included in this study. The following devices were implanted: Medtronic 7217B, 7217D, 7220C, 7221CX, 7223CX, 7227CX, 7229CX, 7271, 7273, 7278 and CPI/Guidant 1600, 1715, 1742, 1790, 1861. We recorded a detailed patient history including any prescriptions and evaluated his/her 12-lead electrocardiogram and transthoracic echocardiogram with doppler screening. The signal-averaged electrocardiogram (SAECG) (Arrhythmia Research Technology model 1200 EPX, Austin, TX, USA) was also examined. This system constituted a vector magnitude with a bidirectional bandpass filter setting of 40–250 Hz combined with the standard bipolar orthogonal (X, Y, Z) leads. Signal averaging of 200–300 beats was performed to obtain a diastolic noise level of <0.5 μV. The onset and offset of the QRS complex were determined by an algorithm that calculated the total QRS duration (TQRSD), root mean square voltage of the last 40 ms of the QRS complex (RMS40) and the duration of the terminal low amplitude signals of <40 μV of the QRS complex (LAS40). Coronary angiography was performed in all patients to rule out ischemic cardiomyopathy. Endocardial biopsy was conducted in 42 patients after obtaining informed consent. The left ventricular ejection fraction (LVEF) was assessed by using radionuclide scanning or left ventriculography. Patients with diffuse left ventricular dysfunction and enlargement of the left ventricle were defined as having DCM when coronary artery disease, valvular disease, or any other cardiomyopathy was excluded.

The study patients received an ICD for secondary prevention of sudden cardiac death after 1 or more episodes of confirmed sustained ventricular tachyarrhythmias or under the context of any presumed tachyarrhythmic syncopal attacks with induction of VT/VF during an electrophysiological study. Single-chamber devices were implanted in 24 (42%) patients and 29 (58%) patients had dual-chamber devices. The ICD was programmed according to the documented or induced arrhythmia with at least 2 detection zones. The lowest VT-detection zone had a cycle length of 419±55 ms. In the VT-zone, anti-tachycardia pacing including more than 1 burst pacing and/or 1 ramp pacing therapy followed by cardioversion were programmed, whereas maximum shocks were programmed in the VF-zone.

Table 1. Baseline Characteristics of the Study Population (n=53)

Clinical characteristics	
Age (years)	55±15
Gender (male) (%)	41 (77%)
BMI (kg/m^2)	21±2.9
NYHA classification	1.8±0.8
Creatinine clearance (ml/m)	74±29
Hospitalization for preceding HF (%)	29 (55%)
History of AF before ICD implantation (%)	17 (32%)
Monomorphic VT as index arrhythmia (%)	35 (66%)
LVEF (%)	27±10
Baseline ECG	
QRS-width (ms)	129±40
QT-intervals (ms)	494±67
Signal-averaged ECG	
TQRSD (ms)	158±48
LAS40 (ms)	55±28
RMS40 (μV)	18.7±17.7
Echocardiography	
LADs (mm)	41±9
LVDd (mm)	67±10
LVDs (mm)	56±12
Medication	
β-blocker (%)	43 (81%)
Amiodarone (%)	27 (56%)
Digitalis (%)	25 (47%)
Spironolactone (%)	25 (47%)
ACE-inhibitor (%)	40 (75%)
Diuretics (%)	38 (72%)
Class I antiarrhythmics (%)	5 (9%)

BMI, body mass index; NYHA, New York Heart Association; HF, heart failure; AF, atrial fibrillation; ICD, implantable cardioverter defibrillator; VT, ventricular tachycardia; LVEF, left ventricular ejection fraction; ECG, electrocardiogram; TQRS, total filtered QRS duration; LAS40, the duration of the terminal low (<40 μV) amplitude signals; RMS40, the root mean square voltage of the last 40 ms; LADs, left atrial diameter of end-systole; LVDd, left ventricular diameter of end-diastole; LVDs, left ventricular diameter of end-systole; ACE, angiotensin-converting enzyme.

Definition of ES and Data Collection

For the purpose of this analysis, we defined ES as the occurrence of at least 3 separate episodes of VT/VF terminated by an ICD intervention within a 24-h period.[8] ICD interventions included antitachycardia pacing, low-energy shocks and high-energy shocks. Repetitive ineffective shocks were not categorized as ES. The follow-up began after the implantation and ended in December 2004. The patients visited the ICD outpatient clinic routinely every 3–6 months and were encouraged to schedule additional visits whenever shocks, palpitations, syncope or pre-syncope had occurred. During each visit, the device was interrogated to evaluate the number and type of episodes with the stored electrograms. In the cases with ES, the patient was admitted to the hospital and blood samples (electrolytes, blood cell count, thyroid, creatinine levels, C-reactive protein, creatinine kinase and troponin), echocardiography and coronary angiography were performed if necessary to investigate the causes.

Statistics

P-values of less than 0.05 were considered statistically significant. The results are expressed as frequencies and percentages for categorical variables and median or mean±SD for numerical variables. Univariate Cox proportional hazards models were used to assess the significance of baseline variables with respect to the outcome. Parameters with P<0.10 by univariate analysis were included in a Cox proportional hazards multivariate regression analysis and then adjusted for age, sex, left ventricular diastolic diameter (LVDd) and LVEF. The relationship between the clinical predictors and the occurrence of ES were analyzed by means of survival analysis techniques. The survival function was computed as the time of the implantation to the occurrence of ES. The observation was censored at the time of the last known follow-up or time of death, when ES did not occur. Event-free survival curves were calculated according to the Kaplan-Meier method. The relationship between the occurrence of ES and the prognosis was similarly analyzed. A log rank test was used to determine whether significant differences existed between the curves. A statistical analysis was performed using JMP 5.1 software.

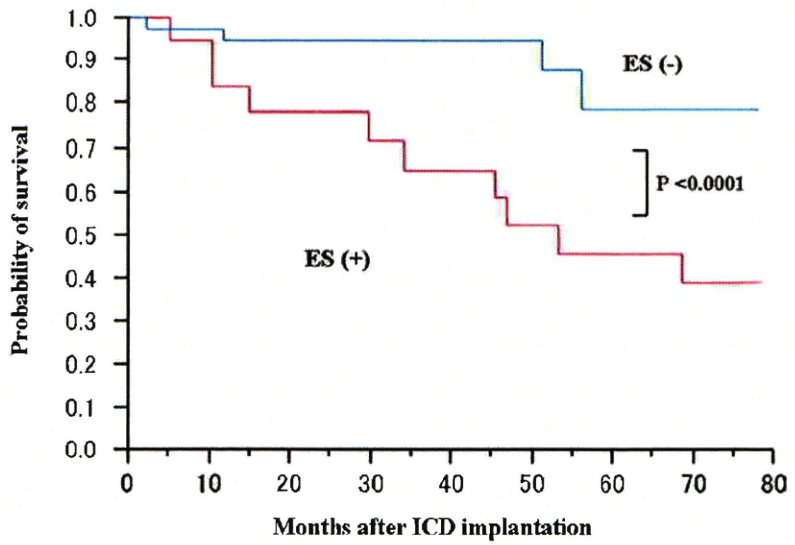

Figure 1. The cumulative probability of survival for dilated cardiomyopathy patients with electrical storm (ES) and those without ES. There was a significant difference in survival between the 2 groups (P<0.0001). ICD, implantable cardioverter defibrillator.

Table 2. Comparison of Baseline Characteristics Between the Patients With ES and Without ES

Patients	Patients with ES (n=18)	Patients without ES (n=35)	Univariate analysis P-value	Multivariate analysis P-value (HR, 95%CI)	Multivariate analysis P-value (HR, 95%CI)
Clinical characteristics					
Age (years)	56.6±14.2	53.6±15.7	0.23		
Sex (male) (%)	14 (77.8%)	27 (77.1%)	0.91		
BMI (kg/m^2)	20.5±2.10	21.9±3.0	0.11		
NYHA classification	2.1±0.8	1.7±0.8	0.058		
Creatinine clearance (ml/m)	78.9±28.6	72.0±28.6	0.82		
Hospitalization for preceding HF (%)	13 (72%)	16 (46%)	0.041		
History of AF before ICD implantation (%)	11 (61%)	6 (17%)	0.0004	0.021 (HR 2.2, 95%CI 1.1–4.5)	0.015 (HR 2.4, 95%CI 1.2–5.7)
Monomorphic VT as index arrhythmia (%)	15 (83%)	20 (57%)	0.04		
LVEF (%)	27.0±9.6	27.3±11.8	0.97		
Baseline ECG					
QRS-width (ms)	137±40	125±39	0.12		
QT-duration (ms)	494±57	496±73	0.87		
Signal-averaged ECG					
TQRSD (ms)	180±47	147±42	0.022		
LAS40 (ms)	76.8±18.3	43.8±24.9	0.0003	0.0049 (HR 1.4/10 ms increase, 95%CI 1.1–2.1)	–
RMS40 (μV)	5.2±3.1	25.9±18.4	<0.0001	–	0.0010 (HR 0.88/1 μV increase, 95%CI 0.77–0.96)
Echocardiography					
LADs (mm)	41.4±9.3	40.4±9.2	0.46		
LVDd (mm)	69.8±10	65.6±9.5	0.11		
LVDs (mm)	59.3±10.2	54.8±12.5	0.11		
Medication					
β-blocker (%)	14 (78%)	29 (83%)	0.57		
Amiodarone (%)	7 (39%)	20 (57%)	0.39		
Digitalis (%)	9 (50%)	16 (46%)	0.59		
Spironolactone (%)	9 (50%)	16 (46%)	0.59		
ACE-inhibitor (%)	13 (72%)	27 (77%)	0.84		
Diuretics (%)	15 (83%)	23 (66%)	0.12		
Group I antiarrhythmics (%)	2 (11%)	3 (9%)	0.16		

ES, electrical storm; HR, hazard ratio; CI, confidential interval; TQRSD, TQRS duration. Other abbreviations see in Table 1.

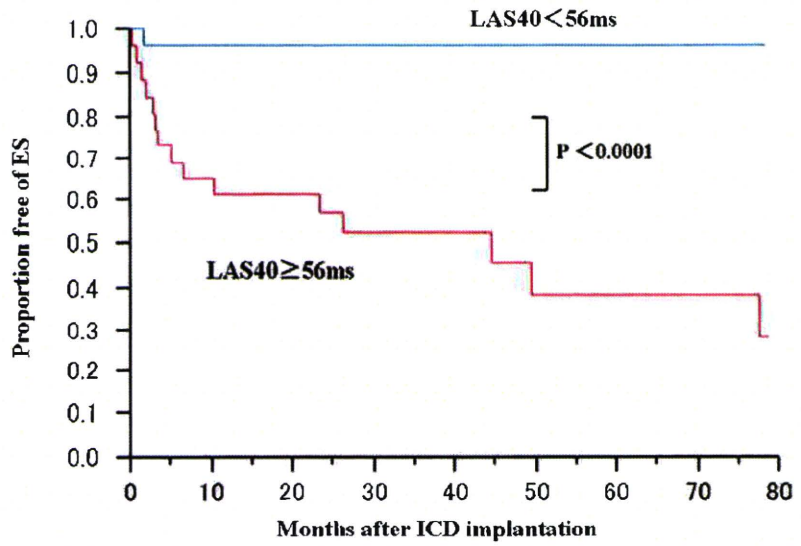

Figure 2. The cumulative probability of freedom from electrical storm (ES) events in dilated cardiomyopathy (DCM) patients with or without terminal low amplitude signals of <40 μV (LAS40) ≥56 ms. The DCM patients with LAS40 ≥56 ms had a significantly higher risk of ES occurrence compared with those with LAS40 <56 ms (P<0.0001). ICD, implantable cardioverter defibrillator.

Results

Baseline Characteristics

The baseline characteristics of the 53 consecutive DCM patients are outlined in **Table 1**. All patients received ICD as a secondary prevention. At the time of implantation, the patients were 55±15 years old. They had a mean LVEF of 27% (9–50%) and a mean LVDd of 67 mm (52–94 mm). The mean NYHA class at the time of the ICD implantation was 1.8±0.8 and the creatinine clearance was 74±29 ml/min. Seventeen (32%) patients had a history of atrial fibrillation (AF). Before ICD implantation, spontaneous VTs were documented in 35 (66%) patients and VF in the remaining 20 (34%) as index arrhythmias. Inappropriate shock therapies were observed in 14 (26%) patients due to sinus tachycardia in 8 (15%) patients, AF in 4 (7.5%) patients and other reasons in 2 (3.5%) patients. As for the medications, β-blockers were prescribed in 43 (81%) patients and amiodarone in 27 (56%).

ES

During a mean follow-up of 52±34 months (median 46 months, range 2–158 months), a total of 18 (34%) patients experienced at least 1 ES episode (median 2 ES episodes per patient). Eleven (61%) patients of the 18 patients with ES experienced 2 or more ES episodes. In 5 (27%) patients, ES was the first episode of an appropriate ICD therapy. The mean duration between the first ES occurrence and ICD implantation was 24±31 months. Three (17%) patients had an exacerbation of their heart failure and the other patients had "extrinsic" causes: 3 (17%) patients had diarrhea or a low potassium level, 2 had an infection and 1 had discontinued the drug therapy. However, no clinical cause could be identified in 9 (50%) patients.

Figure 1 shows the cumulative probability of survival in the DCM patients with ES and in those without ES. As demonstrated, there was a significant difference in the survival between the 2 groups (P<0.0001) and the cumulative mortality for the DCM patients with ES after 60 months was 59%.

Risk Factors for ES

Table 2 shows the baseline characteristics of the subjects with and without ES, and the result of univariate and multivariate analysis. Using a univariate Cox proportional analysis, the NYHA classification at the time of the ICD implantation, history of any previous heart failure, history of AF before ICD implantation, monomorphic VT as index arrhythmia and the parameters on SAECG including LAS40, RMS40 and TQRSD showed the significant association with ES. The correlation between RMS40 and LAS40 was so strong that we were not able to include these 2 parameters in the multivariate analysis simultaneously. When we included LAS40 in the multivariate analysis, a history of AF before ICD implantation and a longer duration of LAS40 remained (P=0.021 and 0.0049, respectively), and when we included RMS40 in the multivariate analysis, a history of AF before ICD implantation and a lower value of RMS40 remained as the significant predictors of ES occurrence (P=0.015 and 0.001, respectively), after adjustment for age, sex, LVDd and LVEF. No independent significant relationships were observed between NYHA classification at the time of the ICD implantation, history of any previous heart failure, monomorphic VT as index arrhythmia or value of TQRSD and the occurrence of ES.

Predictors of ES

Using a sensitivity-specificity analysis utilizing a receiver operating characteristic curve, the cut-off value of LAS40 and RMS40 was set at 56 ms and 11.7 μV to optimize the capability to predict ES. In cases with a cut-off value of LAS40 setting at 56 ms and RMS40 at 11.7 μV, using LAS40 predicted ES with a sensitivity of 94% and specificity of 74%. The areas under the curve of LAS40 at 56 ms was slightly larger than that of RMS40 at 11.7 μV (0.87 vs 0.84, respectively). The Kaplan-Meier curves of the freedom from ES event between the group with or without LAS40 ≥56 ms are illustrated in **Figure 2**. The DCM patients with LAS40 ≥56 ms had a significantly higher risk of ES occurrence compared with those with LAS40 <56 ms (P<0.0001). The Kaplan-Meier curves of the freedom from ES event between

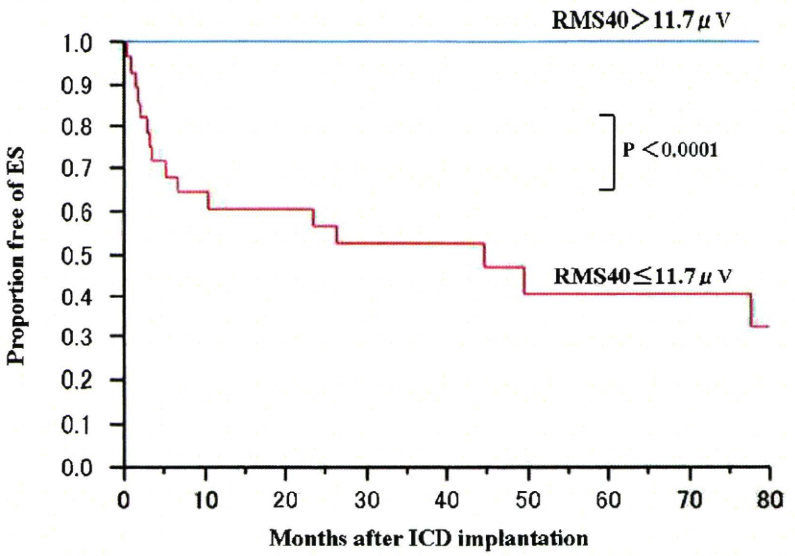

Figure 3. The cumulative probability of freedom from electrical storm (ES) events in dilated cardiomyopathy (DCM) patients with or without root mean square voltage of the last 40 ms of the QRS complex (RMS40) ≤11.7 μV. The DCM patients with RMS40 ≤11.7 μV had a significantly higher risk of ES occurrence compared with those with RMS40 >11.7 μV (P<0.0001). ICD, implantable cardioverter defibrillator.

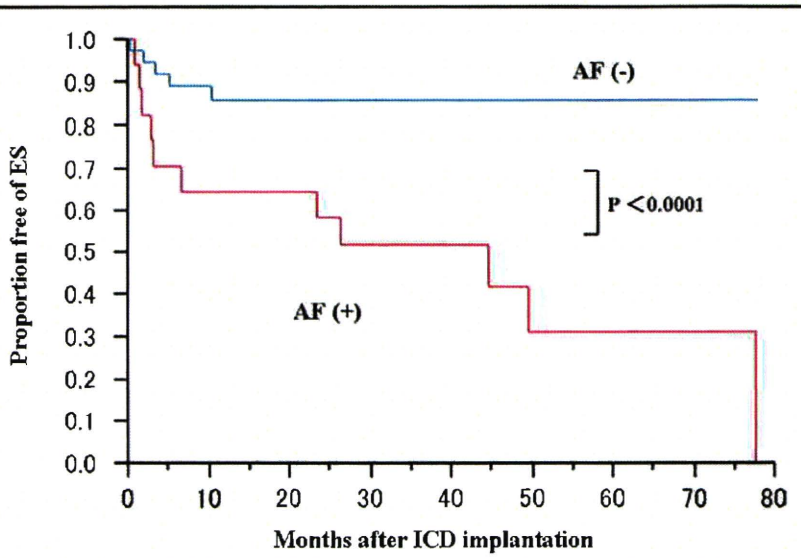

Figure 4. The cumulative probability of freedom from electrical storm (ES) events in dilated cardiomyopathy (DCM) patients with or without a history of atrial fibrillation (AF) before an implantable cardioverter defibrillator (ICD) implantation. The DCM patients with a history of AF before ICD implantation had a significantly higher risk of ES occurrence compared with those without a history of AF before ICD implantation (P<0.0001).

the group with or without RMS40 ≤11.7 μV are shown in Figure 3. The DCM patients with RMS40 ≤11.7 μV had a significantly higher risk of ES occurrence compared with those with RMS40 >11.7 μV (P<0.0001). Furthermore, the Kaplan-Meier curves of the freedom from ES event between the groups with and without a history of AF before ICD implantation showed that the DCM patients with a history of AF before ICD implantation had a significantly higher risk of ES occurrence compared with those without a history of AF before ICD implantation (P<0.0001) (Figure 4). Atrial fibrillation plus 2 of the following parameters could significantly predict the occurrence of ES: SAECG, LAS40 ≥56 ms or RMS40 ≤11.7 μV. As Figure 5 shows, when using the combination of these independent predictors (AF and LAS40 ≥56 ms, or AF and RMS40 ≤11.7 μV), the study population could be stratified into 3 groups according to the risk of ES before the implantation.

Discussion

The main finding of our study was that both the quantitative value of the SAECG, especially the value of LAS40, RMS40 and a history of AF before ICD implantation could independently predict the occurrence of ES.

SAECG as a Predictor of ES

Regarding the SAECG, longer LAS40 and lower RMS40 remained a significant index for predicting the occurrence of ES by multivariate analysis, although all 3 parameters on the SAECG; longer LAS40, lower RMS40 and longer TQRSD, were significant by univariate analysis. The risk of ES increased by 40% for each additional 10 ms increase in the value

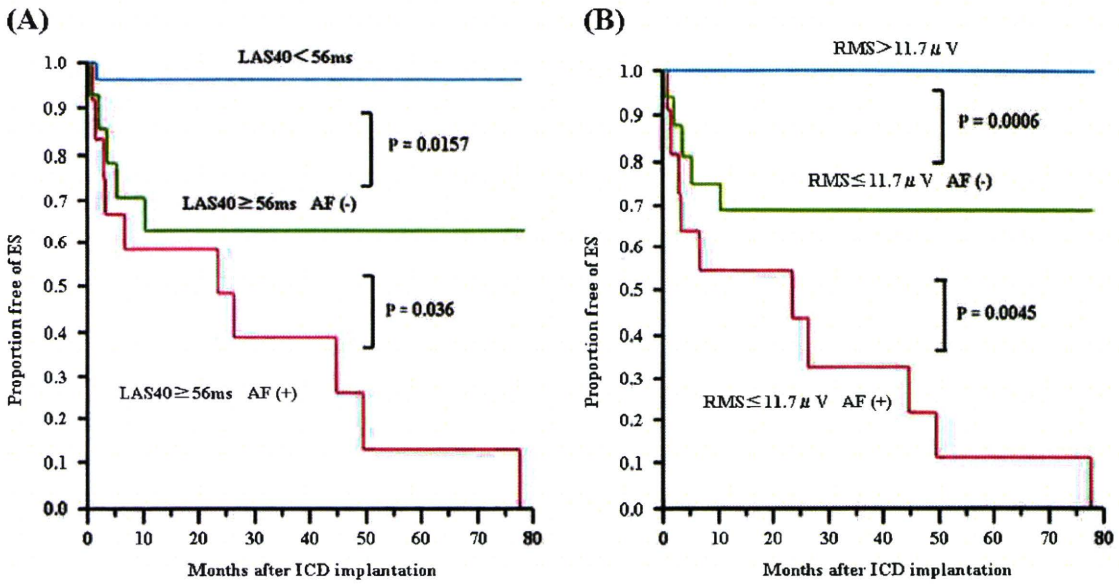

Figure 5. The risk stratification for electrical storm (ES) events with the combination of terminal low amplitude signals of <40 μV (LAS40) or root mean square voltage of the last 40 ms of the QRS complex (RMS40) and a history of atrial fibrillation (AF) before implantable cardioverter defibrillator (ICD) implantation. The combination of (**A**) LAS40 ≥56 ms and a history of AF before ICD implantation or (**B**) RMS40 ≤11.7 μV and a history of AF before ICD implantation could stratify the risk of ES events.

of LAS40 (HR 1.4/10 ms increase, 95% confidence interval (CI) 1.1–2.1; P=0.0049). The optimized cut-off value of LAS40 determined from the receiver operating characteristic curve for differentiating the patients with ES from those without ES was 56 ms, which gave a sensitivity of 94%, specificity of 74%, positive predictive value of 65% and negative predictive value of 96%. In contrast, the risk of ES decreased by 12% for each additional 1 μV increase in the value of RMS40 (HR 0.88/1 μV, 95%CI 0.77–0.96; P=0.001). The optimized cut-off value of RMS40 determined from the receiver operating characteristic curve for differentiating the patients with ES from those without ES was 11.7 μV, which gave a sensitivity of 100%, specificity of 71%, positive predictive value of 61% and negative predictive value of 100%. We used the optimized cutoff value of LAS40 as 56 ms and RMS40 as 11.7 μV to stratify the risk of ES. However, the cut-off value of LAS40 was usually set at 38 ms and RMS40 at 20 μV. We also evaluated the significance of the SAECG for predicting the occurrence of ES by using the cut-off value of LAS40 at 38 ms and RMS40 at 20 μV, and it was possible to differentiate the patients with ES from those without ES by using these classical values as well.

Although the significance of the SAECG as a predictor of ES has never been reported thus far, there have been several reports that have indicated the significance of the SAECG as a predictor of ventricular tachyarrhythmias or the prognosis in DCM patients.[10–16] Goedel-Meinen et al reported that an abnormal SAECG was an independent indicator for sudden cardiac death (3.7-fold risk), the total cardiac mortality (2.1-fold risk) and any cardiac events (2-fold risk) in patients with DCM using a multivariate analysis.[12] Mancini et al showed the effectiveness of SAECG as an independent predictor of end points including death, urgent transplant and VT in patients with non-ischemic congestive cardiomyopathy and relative risk estimate (actually an odds ratio) for abnormal vs normal SAECG was 16.7:1 for these events in this report.[10]

The SAECG is a modality for assessing the existence of ventricular late potentials, which indicate an arrhythmic substrate, especially depolarization abnormalities, leading to sustained ventricular tachyarrhythmias. In general, ventricular late potentials may be defined as low-amplitude fractionated activity appearing at the end of QRS and extending into the ST-segment. Fragmented electrocardiograms are thought to be found when myocardial fibers are separated by connective tissue. Moreover, a close correlation between the presence of continuous fractionated electrical activity and the perpetuation of VT has been demonstrated.[17,18] The extent of the myocardial fibrosis also appears to be correlated with an abnormal SAECG. Yamada et al reported that patients with biopsy-proven marked fibrosis exhibited a longer TQRSD and lower LAS40 than did the patients with less fibrosis, although those patients had no differences in the left ventricular end-diastolic dimension and ejection fraction.[19] This relation was also confirmed in a study by Konta et al, which demonstrated that patients with DCM had abnormal thallium perfusion images.[20] These principles could support the theory that the late potentials could contribute to the maintenance of the electrical instability, thus increasing the possibility of the occurrence of ES. The myocardium in the patients with ES would be more damaged with more severe late potentials, and thus the conventional cut-off value (TQRSD >120 ms, RMS40 <20 μV and LAS40 >38 ms) would not be adequate for specifically predicting ES.[21–25]

A History of AF Before ICD Implantation as a Predictor of ES

Our study showed that a history of AF before ICD implantation was a strong independent predictor of the occurrence of ES (HR 2.3, 95%CI 1.2–5.0; P=0.013). Although there have

been no reports assessing the significance of a history of AF before ICD implantation as a predictor of ES thus far, its significance as a predictor of ventricular arrhythmias has been reported in previous studies.[26–28] Moreover, Grimm et al reported that AF, the LVEF and a history of VT/VF before an ICD implantation were the predictors for an appropriate ICD intervention in DCM patients during 36 months of follow-up.[29]

Because ES is considered to be one of the most severe cases of ventricular tachyarrhythmias, it is not unreasonable that AF could be one of the predictors of ES as the result of our study. There are several possible explanations for the association between a history of AF before ICD implantation and ventricular tachyarrhythmias including ES. First, a rapid ventricular rate during AF will directly reduce the ventricular refractoriness and, moreover, the irregular rhythm during both paroxysmal and persistent AF leads to a high incidence of short-long-short sequences, which could have a pro-arrhythmic effect. Second, AF decreases the cardiac output and increases the filling pressure through the loss of an atrial effective contraction and decreased diastolic time, which could affect the electrophysiological properties. Third, AF could trigger ischemia, through a tachycardia, also leading to a reduction in the cardiac output and increasing the left ventricular filling pressure or directly changing the electrophysiological properties of the ventricles.[27,30–34]

To the best of our knowledge, the only study that referred to ES with DCM patients was published by Bansch et al.[1] They reported that the presence of NYHA III heart failure before an ICD implantation, low LVEF (<40%), a history of monomorphic VT or inducibility of monomorphic VT, especially that with a superior axis, were the best predictors of ES in patients with DCM.[1] Unlike that study, the LVEF did not remain as a significant risk factor in the present study. The baseline LVEF was tightly distributed at much lower levels between the 2 groups with and without ES in our study, so that the difference in the LVEF between each patient could fall into obscurity. Although heart failure and monomorphic VT remained as significant predictors of ES by univariate analysis, they did not remain so by multivariate analysis. The difference in the study population, the severity of any underlying disease or the definition of ES could be part of the reason for the discrepancies with previous studies.[1,8,35,36]

Potential Approaches to Prevent ES

Potential approaches were considered to prevent ES. First, recent reports revealed that novel empiric ablation techniques for substrate modification and prevention of VT/VF could reduce the ICD therapy,[37,38] and cardiac resynchronization therapy could reduce the incidence of VT due to reverse remodeling.[39,40] Pulmonary vein isolation may be 1 of the options to prevent ES by suppression of AF.[41]

Study Limitations

First, the retrospective observational design was a major limitation of our study. Furthermore, the accurate classification of shocks as being appropriate or inappropriate remains a problem, especially for patients with a single-chamber ICD. Because patients with a history of AF before ICD implantation were more likely to have single-chamber ICDs, there may have been more false positive events in the history of the AF group. However, the ICD electrograms were carefully examined by 2 expert electrophysiologists blindly to confirm that inappropriate therapy was not a trigger of these ESs and to determine the appropriateness of the ICD shocks.

Second, because the number of patients in the study group was small, the statistical power of the patient group analyses may therefore be limited. However, the study group was relatively homogeneous because all consecutive secondary prevention patients were included.

Third, cardiac resynchronization therapy with a defibrillator function should be used in our study population, which would reduce the occurrence of ES at this moment. However, cardiac resynchronization therapy with a defibrillator function was not available in Japan back then.

Conclusion

ESs occur frequently in ICD patients with DCM. The major predictors of ES were a longer LAS40, a lower RMS40 and a history of AF before ICD implantation. The combination of these indices could effectively stratify the risk of ES prior to the ICD implantation.

Disclosure

Conflict of interests and statement: no financial support from a specific company was given and there was no conflict of interest or specific unapproved usage of any compound or product.

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Long QT syndrome with compound mutations is associated with a more severe phenotype: A Japanese multicenter study

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BACKGROUND: Long QT syndrome (LQTS) can be caused by mutations in the cardiac ion channels. Compound mutations occur at a frequency of 4% to 11% among genotyped LQTS cases.

OBJECTIVE: The purpose of this study was to determine the clinical characteristics and manner of onset of cardiac events in Japanese patients with LQTS and compound mutations.

METHODS: Six hundred three genotyped LQTS patients (310 probands and 293 family members) were divided into two groups: those with a single mutation (n = 568) and those with two mutations (n = 35). Clinical phenotypes were compared between the two groups.

RESULTS: Of 310 genotyped probands, 26 (8.4%) had two mutations in the same or different LQTS-related genes (compound mutations). Among the 603 LQTS patients, compound mutation carriers had significantly longer QTc interval (510 ± 56 ms vs 478 ± 53 ms, $P = .001$) and younger age at onset of cardiac events (10 ± 8 years vs 18 ± 16 years, $P = .043$) than did single mutation carriers. The incidence rate of cardiac events before age 40 years and use of beta-blocker therapy among compound mutation carriers also were different than in single mutation carriers. Subgroup analysis showed more cardiac events in LQTS type 1 (LQT1) and type 2 (LQT2) compound mutations compared to single LQT1 and LQT2 mutations.

CONCLUSION: Compound mutation carriers are associated with a more severe phenotype than single mutation carriers.

KEYWORDS Compound; Gene; Long QT syndrome; Mutation

ABBREVIATION QTS = long QT syndrome

(Heart Rhythm 2010;7:1411–1418)

Introduction

Congenital long QT syndrome (LQTS) is a heterogeneous disease characterized by prolonged ventricular repolarization and episodes of syncope and/or life-threatening cardiac arrhythmias, particularly polymorphic ventricular tachycardia.[1] Several disease-causing genes have been identified, including genes encoding cardiac ion channel-composing proteins, namely, *KCNQ1* (LQT1), *KCNH2* (LQT2), *SCN5A* (LQT3), *KCNE1* (LQT5), *KCNE2* (LQT6), *KCNJ2* (LQT7), and *CACNA1C* (LQT8), and genes encoding a family of versatile membrane adapters, namely, *ANK2* (LQT4), *CAV3* (LQT9), *SCN4B* (LQT10), *AKAPs* (LQT11), and *SNTA1* (LQT12).[2–5] Two modes of inheritance are involved in this syndrome, which exhibits both an autosomal dominant and an autosomal recessive pattern. The majority of LQTS cases are inherited in an autosomal dominant fashion. This pattern, which has been named as Romano-Ward syndrome,[6,7] can result from a single mutation in one

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of the LQTS candidate genes. On the other hand, Jervell and Lange-Nielsen syndrome, which is inherited in an autosomal recessive fashion, is very rare,[8] affecting less than 1% of LQTS cases. It is caused by homozygous or compound heterozygous mutations of *KCNQ1* or *KCNE1*.[9,10]

Genetic analysis sometimes reveals two or more mutations in LQTS patients with clinical phenotypes of Romano-Ward syndrome. These compound mutations were shown to be associated with an increased arrhythmic risk.[11,12] However, most previous studies were conducted in Caucasian patients, and few systematic studies have involved Asian cohorts. In the present study, we analyzed the clinical characteristics of LQTS patients who were registered in a Japanese multicenter study. Analysis of the more 600 genotyped patients revealed that LQTS patients with compound mutations not only were common in Japan (8.4% among probands) but were associated with longer QTc and earlier onset of cardiac events. In patients who initially are diagnosed as LQT1 or LQT2, additional mutations may be present if patients have a more severe phenotype than expected; therefore, conducting a survey for major LQTS-related genes is critically important.

Methods

Patients and data collection

Major candidate genes were analyzed in 612 consecutive and unrelated probands with a suspected clinical diagnosis of congenital LQTS, who were referred to four centers in Japan (Shiga University of Medical Science, Otsu; Kyoto University Graduate School of Medicine, Kyoto; Kanazawa University Graduate School of Medical Science, Kanazawa; and National Cardiovascular Center, Suita) between June 1996 and January 2009. If gene mutations in LQTS-related genes were identified, further genetic analysis was conducted among family members as extensively as possible. All patients in the cohort were Japanese.

Genetic analysis

Informed consent was obtained from all individuals or their guardians according to standards established by the local institutional review boards. Genotypic and DNA sequence analyses of *KCNQ1, KCNH2, SCN5A, KCNE1,* and *KCNE2* were performed as described previously.[13] In addition, *KCNJ2* (Andersen syndrome [LQT7][14,15]) was analyzed in patients who had not only QT prolongation but also the clinical phenotype of Andersen syndrome, for example, periodic paralysis or dysmorphic features. Other candidate genes (e.g., ankyrin-B [LQT4], *CACNA1C* [Timothy syndrome, LQT8]) were not analyzed because mutations in these genes are extremely rare. Denaturing high-performance liquid chromatography was performed as described previously.[16] Abnormal conformers were amplified by polymerase chain reaction and sequenced using an ABI PRISM310 DNA sequencer (Perkin-Elmer Applied Biosystems, Wellesley, MA, USA). "Splicing error" mutations were defined as those that occurred within three bases of the splicing sites. When mutations were detected, 200 Japanese control subjects were checked and single nucleotide polymorphisms were excluded from the study. If mutations of these genes were detected in the probands, their family members were also analyzed and genotype–phenotype correlations confirmed. Mutation-negative controls were defined as family members without mutations detected in each proband. Nonsynonymous as well as synonymous single nucleotide polymorphisms were excluded with the assistance of data from previous reports[17–19] and from the National Center for Biotechnology Information database.

Clinical characterization

Baseline clinical data were recorded for each patient and included the following: age at diagnosis, age at first cardiac event, sex, cardiac events, family history of sudden cardiac death or LQTS members, ECG measurements, and therapeutic regimens administered. Schwartz scores also were calculated.[20,21] In the analysis of triggers of arrhythmic events, triggers were divided into four categories: exercise/swimming, emotional stress/arousal stress, sleep/rest, and other conditions.

ECG parameters measured at baseline included RR, QT_{end}, QT_{peak}, and $T_{peak\text{-}end}$ ($QT_{end\text{-}peak}$) intervals. The latter is thought to reflect transmural dispersion of ventricular repolarization.[22] Measurements were the mean of at least three beats measured in lead V_5 from the 12-lead ECG during stable sinus rhythm and corrected by the Bazett formula.[23] QT_{end} was manually measured as the time interval between QRS onset (Q) and the point at which the isoelectric line intersected a tangential line drawn at the maximal downslope of the positive T wave or the maximal

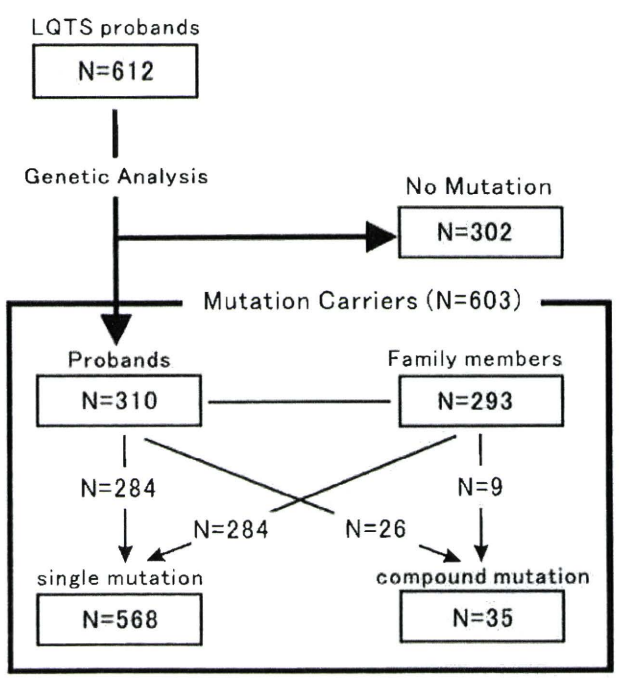

Figure 1 Schematic representation of the positive-mutation carriers in this study. LQTS = long QT syndrome.

Table 1 Overall data of patients with compound mutations

Research groups	Schwartz et al.	Westenkow et al.	Tester et al.	This study
Reported years	2003	2004	2005	2010
The corresponding number in the reference list	25	11	12	
Percentage of probands with compound mutations (probands with compound mutations/total probands) subtypes	4.6% (6/130)	5.2% (9/172*)	10.8% (29/269)	8.4% (26/310)
LQT1	7 (58%)	14 (35%)	30 (52%)	18 (35%)
LQT2	2 (17%)	10 (25%)	15 (26%)	17 (33%)
LQT3	3 (25%)	2 (5%)	13 (22%)	14 (27%)
LQT5-D85N	0 (0%)	10 (25%)	0 (0%)	0 (0%)
vs. single mutation carriers				
QTc interval	NA	prolonged	not significant	prolonged
Cardiac events	NA	frequent	not significant	not significant
Age of onset	NA	NA	younger onset	younger onset

*This table excluded probands with single nucleotide polymorphisms (SNP), NA = not available.

upslope of the negative T wave (QT_{end}). $QT_{end\text{-}peak}$ then was obtained by calculating as QT_{end} minus QT_{peak}.

Statistical analysis

All analyses were performed using the SPSS 16.0 statistical package (SPSS, Inc., Chicago, IL, USA). Data are expressed as mean ± SD. $P < 0.05$ was considered significant. Univariate comparison of parameters between groups was performed by an unpaired t-test. Differences in incidence between groups were analyzed by Chi-square test or Fisher exact probability test. The cumulative probability of a first cardiac event (syncope, torsades de pointes, ventricular fibrillation, cardiac arrest, or sudden death) occurring before age 40 years and before beta-blocker therapy or after beta-blocker therapy was determined by means of the life-table method of Kaplan-Meier, and results were compared using log rank test.[24]

Results

Genetic characteristics of mutations associated with single and compound mutations

Genetic analysis revealed gene mutations in 310 (51%) of 612 probands. The study enrolled 603 genotyped LQTS patients consisting of 310 genotyped probands and their 293 genotyped family members. A flowchart of the genetic diagnosis of the study population is shown in Figure 1.

Of the 310 genotyped probands, 26 (8.4%) had compound mutations. This rate is comparable to the rates in previous reports of Caucasian patients (Table 1). The 26 probands all had two mutations in the LQTS-related genes we examined. These 52 mutations in 26 probands consisted of 45 missense mutations, 4 frameshift mutations, 2 splice-site mutations, and 1 nonsense mutation (see Online Supplemental Data 1). The mutation types of the 284 single mutation carriers were 210 missense mutations, 34 frameshift mutations, 18 splicesite mutations, 12 deletions, 9 nonsense mutations, and 1 insertion mutation (see Online Supplemental Data 2). Therefore, the mutation types were similar between the two groups (Figure 2).

Among the 293 genotyped family members, there were 284 single mutation carriers and 9 compound mutation carriers. In total, 568 patients with a single mutation (284 probands and 284 family members) consisted of 256 with LQT1, 248 with LQT2, 62 with LQT3, and 2 with LQT5. Thirty-five compound mutation carriers (26 probands and 9 family members) consisted of 9 with LQT2 and LQT3, 7 with LQT1 and LQT2, 6 with LQT1 and LQT3, 4 with double LQT1, 3 with double LQT2 mutations, 2 with LQT1 and LQT7, 2 with LQT2 and LQT7, 1 with double LQT3, and 1 with LQT1 and LQT6.

Families associated with compound mutations

In the analysis of family members associated with compound mutations, 28 single heterozygous mutation carriers and 4 obligate single mutation carriers were identified from 9 families, and single mutation carriers had milder clinical phenotypes than compound mutation carriers (Figure 3). Only 2 (6%) of the 32 single mutation carriers had syncope but no torsades de pointes, an incidence lower than that in compound mutation carriers (54% [19/35] patients, $P < .001$). For single heterozygous mutation carriers in compound mutation families, average QTc interval was 442 ± 30 ms, which was longer than that of the 15 mutation-negative controls (408 ± 28 ms, $P = .001$) but significantly shorter than that of compound mutation carriers (510 ± 56 ms, $P < .001$).

Early onset of cardiac events and more severe QT prolongation was observed in patients with compound mutations

Table 2 compares the clinical characteristics of 35 LQTS patients with compound mutation and 568 LQTS patients with a single mutation. The female-to-male ratio was similar between the two groups. However, the incidence of family members associated with double-hit patients was significantly smaller than that with a single mutation (26% vs 50%, $P = .005$). In the ECG analysis of 496 patients with available information, corrected QT interval was significantly longer in compound mutation carriers than in single mutation carriers (510 ± 56 ms vs 478 ± 53 ms, respectively, $P = .001$), whereas other ECG findings, R-R interval, corrected QT_{peak}, corrected $QT_{peak\text{-}end}$, and rates of

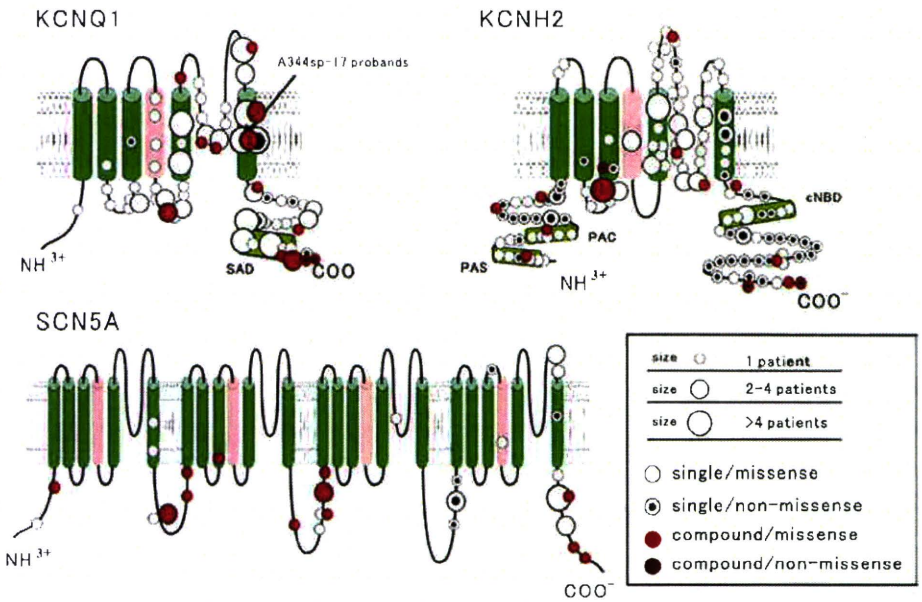

Figure 2 Conventional transmembrane topology of all mutations in the probands.

notched T wave and T-wave alternans were not different between the two groups. The frequency of patients with a normal QTc interval <440 ms was similar between the two groups, whereas the frequency of double-hit patients with QTc intervals >500 ms was significantly higher than in those with a single mutation (66% vs 26%, P <.001). Schwartz scores in the compound mutation group and the rate of patients with a score ≥4 were higher than those in the single mutation group (Schwartz score: 4.3 ± 2.1 vs 3.4 ± 1.9 points, P = .017; rates of Schwartz score ≥4 points: 70% vs 47%, P = .026). A significantly higher number of patients with compound mutations received beta-blocker therapy than did those with a single mutation (56% vs 33%, P = .006).

In the analysis of "all age groups," the frequency of cardiac events was similar between compound and single mutation groups, whereas age at first cardiac event was significantly lower in the compound mutation group (10 ± 8 years vs 18 ± 16 years, P = .043). For the occurrence of syncope or torsades de pointes before age 40 years, compound mutation carriers had significantly more events than did single mutation carriers (54% vs 37%, P = .043). The occurrence of cardiac arrest or ventricular fibrillation was similar between the two groups for patients before age 40 years. In 561 patients with available information on age at first cardiac events, Kaplan-Meier analysis showed that the cumulative rate of survival without a cardiac event before age 40 years and use of beta-blocker therapy differed significantly between compound and single mutation carriers (P = .004 by log rank test; Figure 4A) and between compound mutation carriers and each subgroup of single mutation carriers (P = .004 vs LQT1, P = .018 vs LQT2, P = .001 vs LQT3, by log rank test; Figure 4B). In the analysis of matched subtypes between single and compound mutation carriers, patients with additional mutations in an LQTS subtype had a significantly poorer prognosis than LQT1 alone (P = .001; Figure 5) and LQT2 alone (P = .035) but not LQT3 alone (P = .06).

Discussion

In this multicenter study, the major findings were as follows. (1) LQTS-associated compound mutations in the Japanese population were as common as previously reported in studies of Caucasian patient cohorts. (2) Patients with compound mutations displayed longer QTc and earlier onset of cardiac events. (3) Patients with compound mutations had more cardiac events before age 40 years and more beta-blocker therapy. (4) Subgroup analysis showed more cardiac events in LQT1 and LQT2 compound mutations compared to single LQT1 and LQT2 mutations.

Twenty-six probands (8.4% of genotyped LQTS) were found to have two variants in genes encoding ion channels (*KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2,* or *KCNJ2*). This incidence rate is in general agreement with other studies that reported a prevalence of compound or multiple mutations of 5% to 11% of genotyped LQTS (Table 1).[11,18,25]

Table 1 summarizes the genetic and clinical characteristics of patients enrolled in previous studies and compares them with the characteristics of patients enrolled in the present study. Sanguinetti and colleagues reported that patients with compound mutations not only had longer QT intervals than single mutation carriers but also had more frequent cardiac events.[11] However, Ackerman and colleagues demonstrated that, although compound mutation carriers were diagnosed at a younger age than single mutation carriers, they did not have significantly longer QT intervals.[12] The difference between these results might be explained by half of the 20 compound probands in the cohort of Sanguinetti et al possessing the common *KCNE1-*

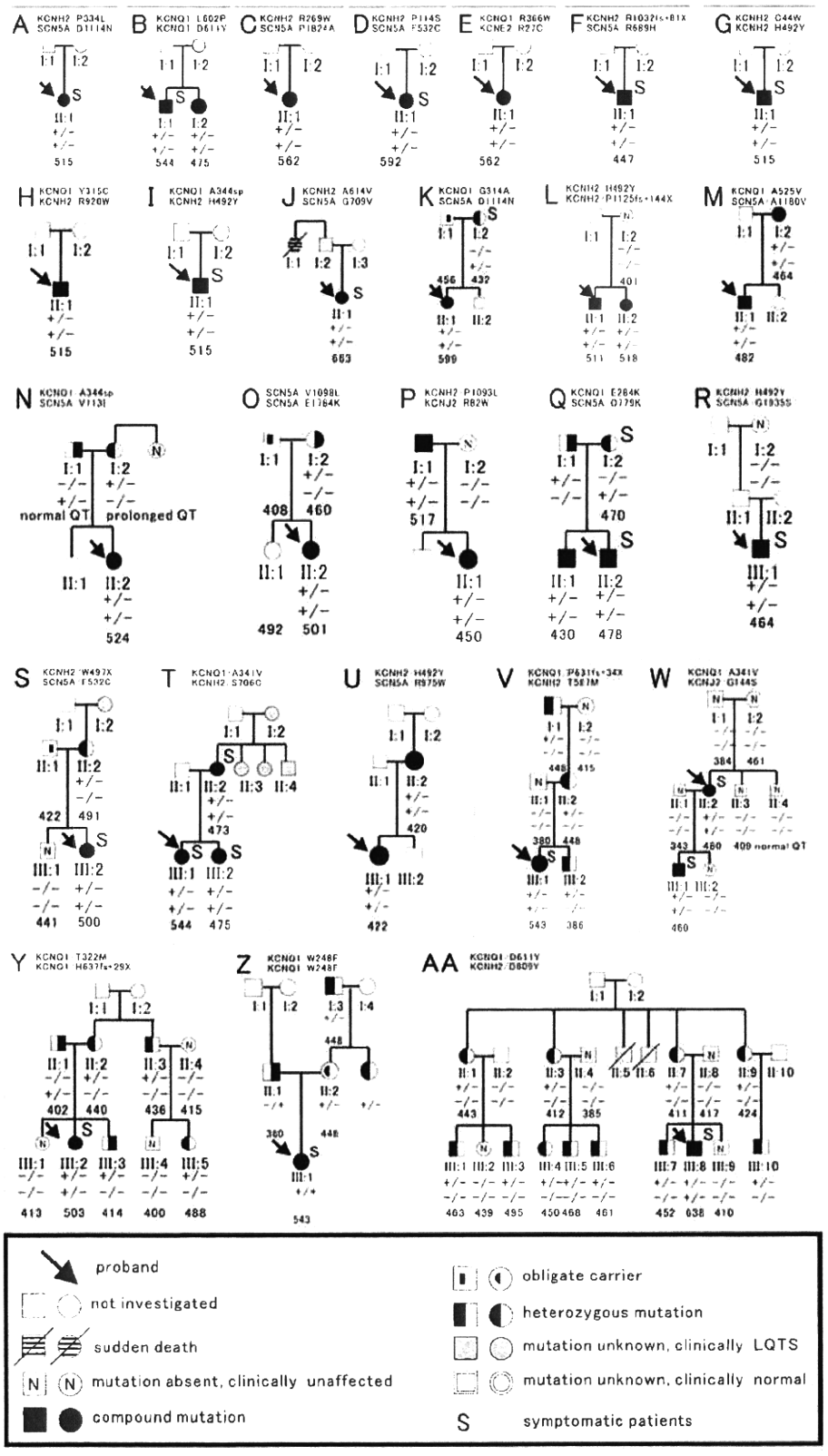

Figure 3 Pedigrees of the families associated with compound mutation probands.

Table 2 Clinical characteristics of LQTS patients with gene mutations

	Compound mutations (N=35)	Single mutations (N=568)	p value
Demographic			
Age at diagnosis (yrs)	19 ± 14 [15, 9–27]	28 ± 19 [22, 12–42]	0.001
Female gender	23 (66%)	330 (58%)	0.394
Proband	26 (74%)	284 (50%)	0.005
Family members	9 (26%)	284 (50%)	0.005
Cardiac events			
cardiac events in all age groups			
Age at first cardiac event (yrs)	10 ± 8 [11, 3.5–13.5]	18 ± 16 [12, 7–19]	0.043
syncope	19 (54%)	235 (41%)	0.161
TdP	10 (29%)	102 (18%)	0.136
cardiac arrest or VF	3 (9%)	44 (8%)	0.748
sudden death	0 (0%)	4 (1%)	1.000
cardiac events before 40 yrs			
syncope or TdP	19 (54%)	205 (37%)	0.043
cardiac arrest or VF	3 (9%)	37 (7%)	0.500
ECG measurements			
RR interval (ms)	866 ± 210	914 ± 174	0.252
corrected QT (ms)	510 ± 56	478 ± 53	0.001
corrected QT >500 ms (%)	23 (66%)	122 (26%)	<0.001
corrected QT <440 ms (%)	3 (9%)	91 (20%)	0.351
corrected QT peak (ms)	385 ± 70	384 ± 50	0.906
corrected QT peak-end (ms)	121 ± 73	95 ± 41	0.081
notched T wave	11 (31%)	200 (37%)	0.540
T-wave alternans	0 (0%)	30 (5%)	0.246
Diagnosis			
Schwartz score	4.2 ± 2.1	3.4 ± 1.9	0.017
Schwartz score ≧4	21 (70%)	219 (47%)	0.026
Therapy			
β-blocker	10 (56%)	175 (33%)	0.006
class Ib antiarrhythmic drugs	3 (9%)	53 (10%)	1.000
pacemaker	1 (3%)	15 (3%)	1.000
sympathectomy	1 (3%)	3 (1%)	0.218
defibrillator	1 (3%)	32 (6%)	0.712

TdP = torsades de pointes, VF = ventricular fibrillation, NS = not significant, corrected QT = QT interval corrected for heart rate with Bazett formula [A, B], A = median, B–C = first interquartile range–third interquartile range.

D85N polymorphism as the "second hit" (Table 1).[11,26] In all age groups of this study, the incidence of cardiac events, such as torsades de pointes or syncope, was similar between single and compound mutation carriers; however, the clinical phenotypes of those with compound mutations before 40 years of age were more serious than in those with a single mutation (Table 2). Thus, phenotypes with compound mutations appear to be more serious than single mutation carriers, regardless of race.

Beta-blocker therapy is first-line treatment for the prevention of cardiac events in LQTS. Beta-blockers have been shown to significantly reduce cardiac events in LQTS patients, especially LQT1 type.[27–29] However, patients with LQT2 or LQT3 have been reported to be less responsive to beta-blocker therapy[27,30] and may require additional therapy, such as pacemaker implantation for LQT2 or a Class Ib antiarrhythmic drug for LQT3. It may be recommended that patients with compound mutations receive additional individual therapy based on their LQTS subtype, for example, the combination of beta-blocker and Class Ib antiarrhythmic drugs for patients with LQT1 and LQT3. In patients who were first diagnosed as LQT1, Kobori et al[31] reported that additional mutations in different LQTS-related genes influenced phenotype severity and reduced beta-blocker effectiveness. Previous reports showed that approximately 20% of LQT1 patients were resistant to beta-blocker therapy. Additional or "latent" mutations may be present in these patients, and conducting a survey for major all LQTS-related genes, even after a possible mutation is identified, is critically important.

Family study analyses are of enormous importance because single mutation carriers in this study tended to have mild phenotypes. Most of the single mutation carriers in families of compound probands remained asymptomatic. However, double hits of these "latent" gene carriers could cause more serious phenotypes.[32,33] Jervell and Lange-Nielsen syndrome is a well-documented LQTS phenotype with an autosomal recessive pattern. The loss of function of I_{Ks} on both alleles generally causes not only more severe clinical phenotypes but also deafness.[9,10] In our study, two of three probands with double *KCNQ1* mutations had no deafness. We speculate that these mutations would functionally cause mild changes without complete loss of I_{Ks}. Westenskow et al[11] reported the molecular mechanism of

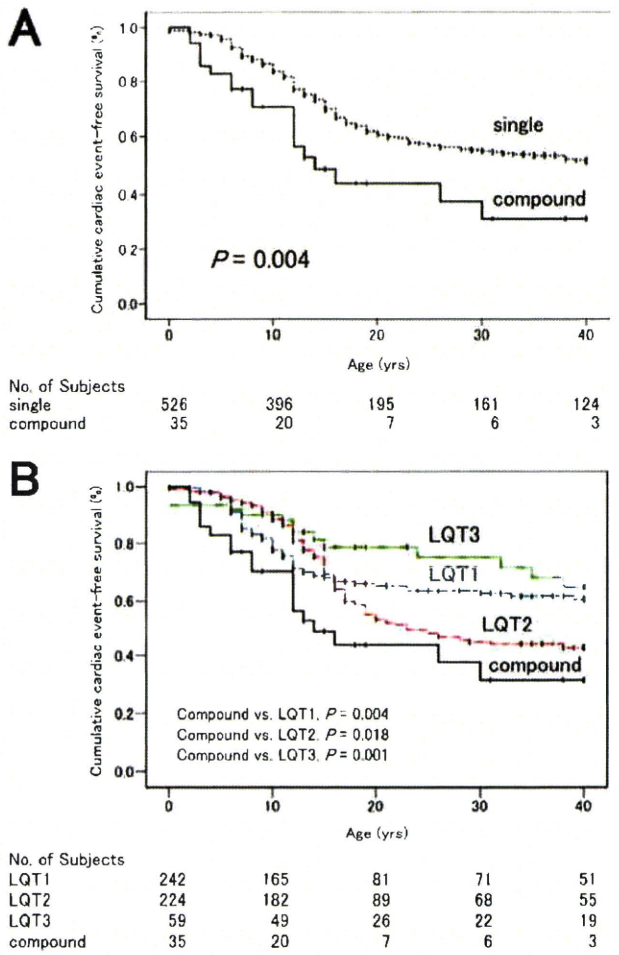

Figure 4 Kaplan-Meier cumulative probability of cardiac event-free survival from birth to age 40 years and before therapy. **A:** Comparison between patients with a single mutation and compound mutations. **B:** Comparison among patients with long QT syndrome type 1 (LQT1), type 2 (LQT2), type 3 (LQT3), and compound mutations.

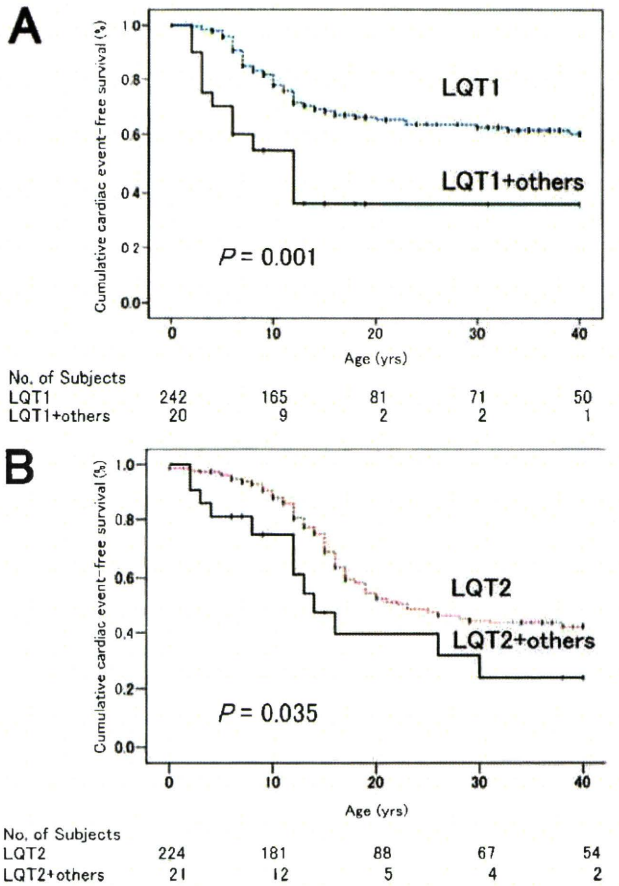

Figure 5 Kaplan-Meier cumulative probability of cardiac event-free survival from birth to 40 years of age and before therapy. **A:** Comparison between patients with long QT type 1 (LQT1_ subtype and compound mutation carriers with LQT1 plus other mutations. **B:** Comparison between patients with long QT syndrome type 2 (LQT2) and those with LQT2 plus other mutations.

increased risk through compound mutations using heterologous expressions in *Xenopus* oocytes. When wild-type and variant subunits were coexpressed in appropriate ratios to mimic the genotype of the probands with mutations, the reduction in current density was equivalent to the additive effects of the single mutations. Coexpression of two mutant subunits caused a significant but incomplete reduction. Thus, either compound mutation seems to be associated with mild functional damage. It is necessary to have "double hits" of these mild mutations in order to produce symptoms.

Study limitations

This study has several limitations. First, six major LQTS candidate genes were examined, but not for minor genes encoding a family of versatile membrane adapters. However, excluding these minor genes from our investigations would not have affected the overall study results, largely because the incidence of these minor gene mutations reportedly is ≤1%. Second, analysis of single mutation carriers in compound mutation families is dominated by their presence in only 35% (9/26) of families. Therefore, there might be a statistical bias due to a mutation-specific effect. Third, Kapa et al[19] reported the need for further studies on whether regions such as the interdomain linker of *SCN5A* could affect the clinical phenotypes of LQTS. In this study, we were able to distinguish mutations from these "genetic noises," especially in the *SCN5A* gene.

Acknowledgment

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Appendix

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.hrthm.2010.06.013.

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ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Relationship Between Oral Amiodarone and Inappropriate Therapy From an Implantable Cardioverter Defibrillator

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Background: This study evaluated the efficacy of amiodarone for avoiding inappropriate therapies by implantable cardioverter defibrillators (ICDs).

Methods and Results: A total of 232 patients with structural heart disease (58±13 years; 78% males) who underwent an initial ICD implantation were retrospectively investigated to compare baseline characteristics and event rates of inappropriate ICD therapy delivery between patients with oral amiodarone therapy (amiodarone group, n=116) and those without (non-amiodarone group, n=116). During a mean follow-up of 29±21 months, inappropriate therapies occurred less frequently in the amiodarone group than in the non-amiodarone group (12% vs 27%, P=0.0068). As a cause of inappropriate ICD therapy, only atrial fibrillation (AF) significantly differed between the groups (3% vs 12%, P=0.01). The results of multivariate logistic regression analysis showed that amiodarone therapy (odds ratio (OR) 0.38, 95% confidence interval (CI) 0.19–0.77, P=0.0073) and no history of spontaneous AF (OR 0.27, 95%CI 0.13–0.57, P=0.0007) were independent predictors of a lower risk of inappropriate ICD therapy.

Conclusions: In the present group of ICD patients with structural heart disease, inappropriate therapy delivery occurred predominantly in those with spontaneous AF and/or without amiodarone. (*Circ J* 2010; **74:** 1302–1307)

Key Words: Amiodarone; Atrial fibrillation; Implantable cardioverter defibrillator; Inappropriate therapy

Several trials have suggested that implantable cardioverter defibrillators (ICDs) are effective not only for secondary prevention, but also for primary prevention of sudden cardiac death in patients with structural heart disease.[1–7] One of the major issues in patients receiving an ICD is the serious psychological reaction to the excessive delivery of appropriate shocks triggered by ventricular tachyarrhythmias, as well as inappropriate shocks triggered by rapidly conducted supraventricular tachyarrhythmias.[8–12] Therefore, an important rationale for adjuvant therapy with antiarrhythmic drugs in patients with an ICD is improving quality of life (QOL) by suppressing both supraventricular and ventricular tachyarrhythmias, as well as providing protection against death from arrhythmias.

Editorial p1290

In the Optimal Pharmacological Therapy in Implantable Cardiovertor defibrillator patients (OPTIC) study, amiodarone plus β-blockers was effective for reducing the number of appropriate and inappropriate shocks from ICDs.[13] The efficacy of amiodarone for reducing inappropriate ICD therapies in patients with structural heart disease has been reported previously[14] and more recently, it was reported that amiodarone is effective for preventing inappropriate ICD therapies in selected patients with atrial fibrillation (AF).[15] However, the exact background to the reduction in inappropriate therapies provided by amiodarone has still not been fully investigated. In the present study, we assessed the efficacy of amiodarone for avoiding inappropriate therapies from ICDs and analyzed the contributing factors to a reduction in inappropriate therapies in patients with structural heart disease.

Methods

Patient Population

All patients who underwent ICD implantation with standard transvenous lead systems were included in our institutional registry from 1990 to 2005. Of 271 consecutive patients, a total of 232 patients (mean age 58±13 years, 79% males) with organic heart disease were studied. All patients had spontaneous sustained ventricular tachycardia (VT)/ventricular fibrilla-

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Table 1. Baseline Patient Characteristics

	Amiodarone group (n=116)	Non-amiodarone group (n=116)	P value
M/F	92/24	90/26	NS
Age ≥65 years	46 (40)	34 (29)	NS
Primary prevention of SCD, n (%)	7 (6)	13 (11)	NS
NYHA class III or IV, n (%)	11 (9)	4 (3)	NS
Prior pacemaker, n (%)	5 (4)	6 (5)	NS
Ischemic heart disease, n (%)	54 (47)	38 (33)	0.044
Atrial fibrillation, n (%)	26 (22)	36 (31)	NS
Paroxysmal or persistent, n (%)	18 (16)	22 (19)	NS
Permanent, n (%)	8 (7)	14 (12)	NS
Hypertension, n (%)	36 (31)	30 (26)	NS
Diabetes mellitus, n (%)	29 (25)	22 (19)	NS
LVEF, %	31±12	40±17	<0.0001
LAD, mm	43±10	40±9	0.026
Total heart beats/day	88,157±16,536	93,463±18,199	0.049
Dual chamber, n (%)	55 (47)	26 (22)	0.0001
Antiarrhythmic agents			
Class Ia, n (%)	0 (0)	8 (7)	0.0069
Class Ib, n (%)	19 (16)	32 (28)	NS
β-blocker, n (%)	65 (56)	66 (57)	NS
Sotalol, n (%)	1 (1)	9 (8)	0.019
ACEI or ARB, n (%)	74 (64)	65 (56)	NS

Data are mean±SD or number of subjects (%).
SCD, sudden cardiac death; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker.

tion (VF) or a history of syncope with an inducible sustained ventricular arrhythmia.

All the patients were categorized according to the administration of amiodarone at the time of ICD implantation. Amiodarone was administered by either the referring physician or in hospital for patients who had frequent, refractory sustained ventricular arrhythmias and/or frequent premature ventricular contractions, and also in whom other antiarrhythmic drugs were not effective or tolerated. One patient with concomitant use of amiodarone and a class Ia drug was excluded from the study. The baseline characteristics and event rates of inappropriate ICD therapies between the amiodarone group and non-amiodarone group were compared. We also assessed the univariate and multivariate predictive variables of inappropriate therapies among all subjects. The mean period of follow-up was 29±21 months.

ICD Implantation and Follow-up

The ICDs were implanted by the standard transvenous approach. Dual-chamber ICD devices were selected if the patients had VT with a long cycle length (>350 ms), a supposed indication for pacemaker implantation, or a history of a supraventricular tachycardia (SVT). The presence of SVT was confirmed from the clinical chart or information obtained from the referral doctors, ambulatory ECG and ECG monitoring during hospitalization. The defibrillation threshold (DFT) was analyzed at implantation and the time of administration of the additional antiarrhythmic drugs. No patients who had received cardiac resynchronization therapy were included in this study.

After hospital discharge, the patients were followed up at the outpatient clinic every 3–6 months or immediately after any ICD shock delivery. The evaluation included a history from the patient and interrogation of the ICD for any arrhythmic events. The stored intracardiac recordings were carefully evaluated by 3 independent experienced cardiologists. ICD delivery for any atrial tachyarrhythmias, including AF, atrial flutter, atrial tachycardia or sinus tachycardia, were defined as inappropriate therapy because of SVT, which was defined by the following algorithm. Tachycardia with a regular and narrow QRS morphology on the stored intracardiac recordings retrieved from the ICD was defined as an atrial tachycardia if it had a sudden onset or no atrioventricular dissociation in patients with a dual-chamber ICD. We defined it as sinus tachycardia if the tachycardia gradually initiated at the beginning of the tachycardia. If it was an irregular tachycardia with a narrow QRS morphology, we defined it as AF.

The adverse effects of amiodarone were also evaluated. Patients were checked every 4 months at the outpatient clinic by laboratory examinations and a chest X-ray.

Statistical Analysis

The clinical outcome was the first episode of an inappropriate ICD event, including shocks or antitachycardia pacing therapy. The results are presented as percentage or the mean±SD, as appropriate. The patients with and without oral administration of amiodarone at the time of ICD implantation were compared with an unpaired Student's t-test. The categorical variables were compared using a chi-square test or Fisher's exact test. The time to the first inappropriate therapy was analyzed by the Kaplan-Meier method. Variables with $P<0.05$ in the univariate test were entered into the multivariate logistic regression analysis to identify the independent predictive variables for inappropriate therapies. The level of statistical significance was set at $P<0.05$.