Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Predictors and Proarrhythmic Consequences of Inappropriate Implantable Cardioverter-Defibrillator Therapy

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Background: Despite the benefits of implantable cardioverter-defibrillator (ICD) therapy, inappropriate shocks can lead to multiple adverse effects. The aim of this study was to clarify the predictors of inappropriate ICD shocks and their proarrhythmic consequences.

Methods and Results: We retrospectively studied 316 consecutive patients who underwent ICD implantation from December 2000 to December 2011. Of them, 70 (22%) experienced inappropriate ICD shocks without proarrhythmia requiring some intervention; 2 patients (0.6%) had proarrhythmic inappropriate ICD therapy by antitachycardia pacing (ATP), thereby calculated to be 0.18% of patients per year. However, they did not have syncope from this inappropriate ATP. Multivariate analysis identified younger age (≤56 years: hazard ratio [HR] 1.68, 95% confidence interval [CI] 1.02–2.77, P=0.043), paroxysmal atrial fibrillation (HR 3.00, 95% CI 1.64–5.31, P=0.0002), stroke (HR 2.23, 95% CI 1.11–4.47, P=0.024), and no diuretic use (HR 1.72, 95% CI 1.03–2.93, P=0.039) as independent predictors of the occurrence of inappropriate ICD shocks.

Conclusions: Young age, paroxysmal atrial fibrillation, stroke, and no use of diuretics were independently associated with inappropriate ICD shocks. Proarrhythmic inappropriate ICD therapy was observed with an annual incidence of 0.18% by ATP. (*Circ J* 2015; **79:** 1920–1927)

Key Words: Antitachycardia pacing; Implantable cardioverter-defibrillator; Inappropriate shock; Paroxysmal atrial fibrillation; Proarrhythmia

Inappropriate implantable cardioverter-defibrillator (ICD) shock is painful for patients because of its sudden onset under unexpected situations, thereby yielding mental distress and worsening quality of life.[1–3] Moreover, subanalysis of MADIT-II and SCD-HeFT implied a 2-fold increased risk of death for patients having inappropriate ICD shocks.[4,5] Therefore, new strategies changing the detection time and zone for ventricular tachycardia (VT)/ventricular fibrillation (VF) have been proposed to reduce inappropriate ICD therapy.[6–9]

Inappropriate ICD therapy including shocks and antitachycardia pacing (ATP) can induce proarrhythmia and syncope. However, data regarding the incidence of syncope and proarrhythmia induced by inappropriate ICD therapy are lacking.[10,11] The present study was aimed to determine the patients at risk of inappropriate ICD shocks and to investigate the proarrhythmic effects and syncope by inappropriate ICD therapy.

Methods

Study Patients

We performed a retrospective review of 316 consecutive patients who underwent initial ICD implantation at Hokkaido University Hospital from December 2000 to December 2011. For each patient, baseline data at the time of ICD implantation were collected from the medical records. These included demography, underlying heart diseases, New York Heart Association (NYHA) functional class, echocardiographic data, comorbidities, and medications.

Information about appropriate and inappropriate ICD shocks was collected in each patient until the end of August 2012. In addition, inappropriate ATP therapy that induced VT/VF was obtained for evaluating the prevalence of proarrhythmic events. VT/VF induced by inappropriate ICD therapy requiring some

Received March 19, 2015; revised manuscript received May 20, 2015; accepted May 31, 2015; released online June 24, 2015 Time for primary review: 11 days

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ISSN-1346-9843 doi:10.1253/circj.CJ-15-0306

Table 1. Patients Characteristics According to Receipt or Not of Inappropriate Shock From ICD

	No inappropriate shock (n=246)	Inappropriate shock (n=70)	P value
Age (years)	59±1	54±2	0.005
Male	195 (79)	53 (75)	0.523
LVEF (%)	43±1	46±2	0.219
NYHA class III–IV	66 (27)	15 (21)	0.744
Primary prevention	68 (28)	15 (21)	0.297
Device			0.139
Single chamber	77 (31)	22 (31)	
Dual chamber	108 (44)	38 (54)	
CRT	61 (25)	10 (14)	
Underlying heart disease			0.796
Ischemic	71 (29)	19 (27)	
Non-ischemic	131 (53)	36 (51)	
PED or CSA	44 (18)	15 (21)	
AF	56 (23)	25 (36)	0.029
Paroxysmal/persistent	30 (54)/26 (46)	18 (72)/7 (28)	0.119
Diabetes mellitus	58 (24)	13 (19)	0.376
Hypertension	60 (24)	12 (17)	0.202
Dyslipidemia	99 (40)	20 (29)	0.075
Hyperuricemia	44 (18)	9 (13)	0.320
Stroke	18 (7.3)	10 (14)	0.070

Data are mean±SE or n (%). AF, atrial fibrillation; CRT, cardiac resynchronization therapy; CSA, coronary spastic angina; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class; PED, primary electrical disease.

Table 2. Pharmacological Therapy

	No inappropriate shock (n=246)	Inappropriate shock (n=70)	P value
Na^+ channel blocker	21 (8.5)	9 (13)	0.276
β-blocker	174 (71)	48 (69)	0.727
Amiodarone	120 (49)	27 (39)	0.131
Ca^{2+} antagonist	33 (13)	13 (19)	0.280
ACEI/ARB	161 (65)	45 (64)	0.857
Digitalis	22 (8.9)	3 (4.3)	0.202
Diuretic	128 (52)	26 (37)	0.028
Aldosterone antagonist	75 (30)	15 (21)	0.138
Nitrate	24 (9.8)	6 (8.6)	0.765
Statin	92 (37)	20 (29)	0.173

Data are n (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

intervention by ICD was defined as proarrhythmia, and any arrhythmia terminated spontaneously was not included. The diagnostic classification of these events, especially appropriate or inappropriate therapy, was made by electrophysiological specialists according to the stored intracardiac electrograms.

Device Programming

In general, device programming was as follows. VF zone detected ventricular events faster than 185–200 beats/min, and an initial therapy was 30 J or more (maximum energy of the device). VT zone detected ventricular events faster than 150–170 beats/min, and 3 sequences of ATP were initially attempted. If the arrhythmia continued, the first shock with an energy ranging 10–20 J and subsequent shocks with maximal energy were delivered until its termination. The first shock in VT zone was always 10 J or more in order to prevent possible proarrhythmia induced by low-energy shocks. In the case of patients with documented slow VT, a detection zone lower than 150 beats/min was sometimes programmed. The device-related detection algorithms such as dual-chamber sensing, and the stability and sudden-onset criteria were usually employed for the discrimination of supraventricular tachycardia.[12] After October 2006, the morphology-based algorithm for detecting VT was used as a nominal setting.[13] The technology of ICD has been developed year by year. To compare the incidence of inappropriate ICD therapy between the "old" patients and the "recent" patients, the study population was divided into 2 groups based on the implantation year, that is, before (the "old" group) and after (the "recent" group) October 2006 (**Figure S1**). The ICD devices were manufactured by Boston Scientific (Marlborough, MA, USA), Medtronic (Minneapolis, MN, USA), or St. Jude Medical (Minneapolis, MN, USA).

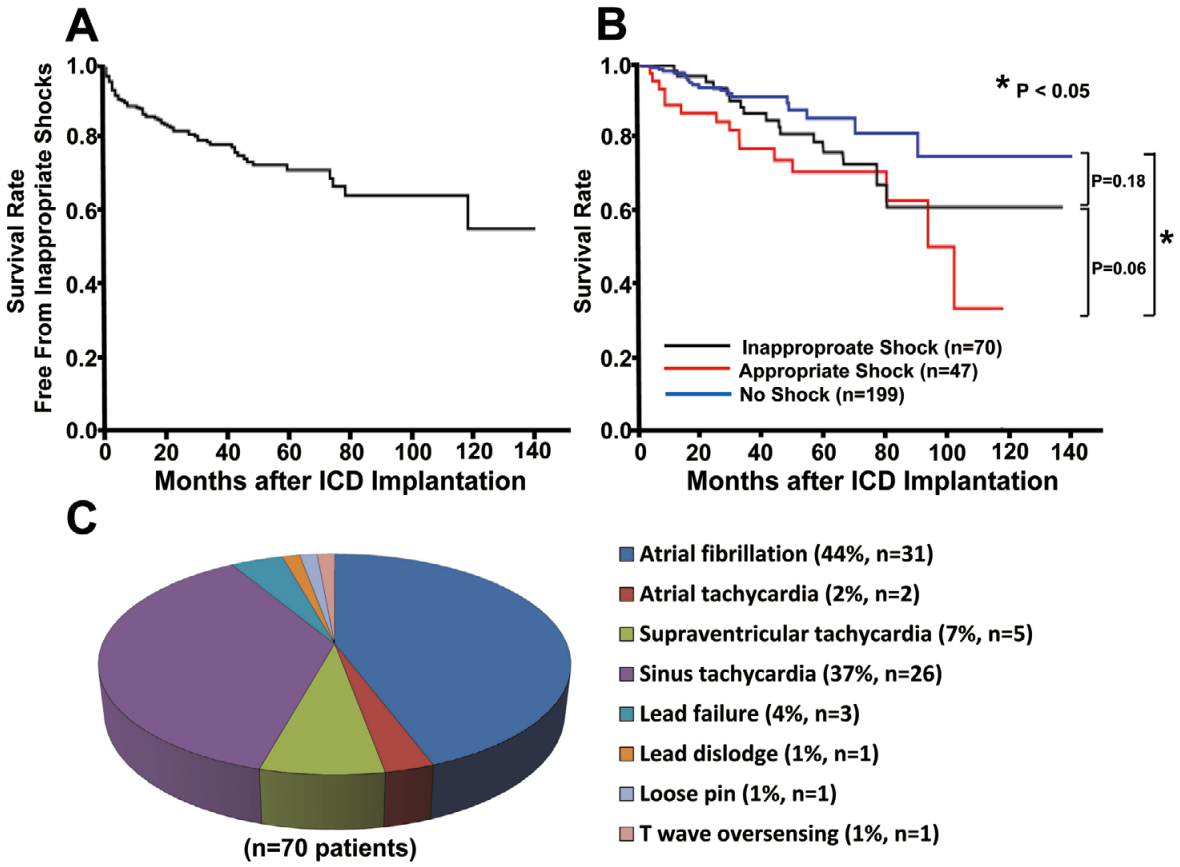

Figure 1. Probability, prognosis and causes of inappropriate shocks from an implantable cardioverter-defibrillator (ICD). (**A**) Kaplan-Meier curve demonstrates survival free of inappropriate ICD shocks. At least 1 inappropriate shock occurred in 70 of 316 patients (22%) during a mean follow-up of 43 months. (**B**) Kaplan-Meier curve demonstrates the overall survival rate in patients with inappropriate shocks (black line), with appropriate shocks (red line), and without any shocks (blue line). Probability of death at 5 year was 24% in the inappropriate shock group. (**C**) Events responsible for first inappropriate shocks (n=70) are summarized.

The study was approved by the Ethics Committee of Hokkaido University Hospital.

Statistical Analysis

All data are expressed as mean±SE. Simple between-group analysis was conducted using Student's t-test. Categorical variables were compared using Fisher's exact test. Cumulative event rates were calculated by using the Kaplan-Meier method. Differences between pairs of survival curves were evaluated by the log-rank test. A Cox proportional-hazards regression model was used to estimate the predictors of inappropriate shock. Differences with $P<0.05$ were considered significant. Statview version 5.0 for Windows (SAS Institute Inc, Cary, NC, USA) was used for all statistical analyses.

Results

Patients Characteristics

Patients characteristics with and without inappropriate shock are given in Table 1. Patients with inappropriate shock were significantly younger. Sex, left ventricular ejection fraction, NYHA functional class, ICD indication, type of device, and underlying heart diseases were comparable between groups. In contrast, the prevalence of atrial fibrillation (AF), especially paroxysmal AF, was higher in patients with inappropriate shock. Dyslipidemia tended to be lower, although it did not reach statistical significance.

Echocardiographic studies demonstrated that left atrial dimension (43±1 mm vs. 45±1 mm), interventricular septum thickness (11.2±0.5 mm vs. 11.8±0.3 mm), left ventricular posterior wall thickness (9.4±0.2 mm vs. 9.8±0.1 mm), and left ventricular end-diastolic dimension (58±1.6 mm vs. 58±0.7 mm) were comparable in patients with and without inappropriate shocks.

Pharmacological therapy in patients with and without inappropriate shock is shown in Table 2. Use of diuretics was significantly lower in the patients who received inappropriate shocks. No differences between groups were found in the use of other medications such as sodium-channel blockers, β-blockers, amiodarone, and calcium antagonists.

Incidence and Causes of Inappropriate Shocks

Of 316 patients, 70 (22.2%) received at least 1 inappropriate shock during the mean follow-up of 43 months; 23 of 70 patients (32.9%) with inappropriate shocks also received appropriate shocks. Figure 1A shows Kaplan-Meier curve of survival free of inappropriate shocks. The probability of inappropriate

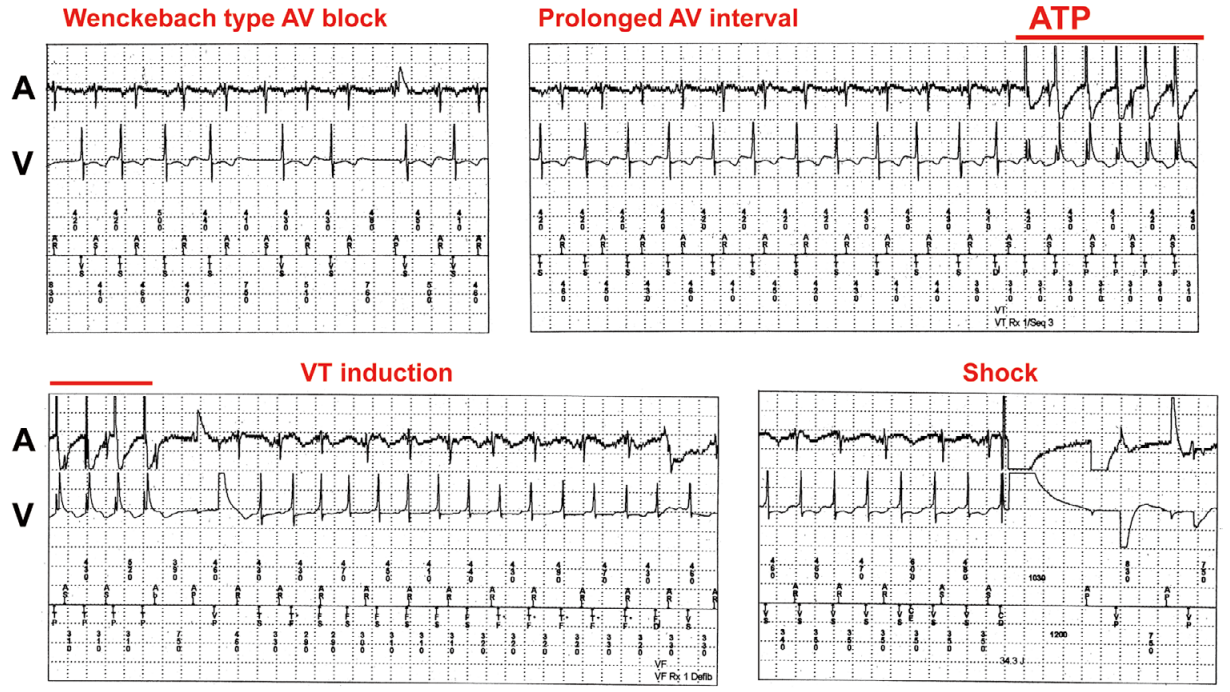

Figure 2. Proarrhythmia induced by inappropriate antitachycardiac pacing (ATP) in an ICD recipient. A 75-year-old patient with dilated cardiomyopathy and a history of sustained ventricular tachycardia (VT) developed sinus tachycardia complicated by variable degree of atrioventricular (AV) block: Wenckebach-type second degree (**Left upper**) and first degree (**Right upper**). The ICD judged it as VT, and subsequent ATP induced VT, which was terminated by high energy (35J) cardioversion (**Lower**). A, atrial electrogram; ICD, implantable cardioverter-defibrillator; V, ventricular electrogram.

shocks was 11.9% at 1 year, 17.6% at 2 years, 21.4% at 3 years, and 28.6% at 5 years after ICD implantation. Figure 1C summarizes the causes responsible for the first inappropriate shock in each patient. Two major causes were AF (n=31, 44.3%) and sinus tachycardia (n=26, 37.1%).

Prognostic Significance of ICD Shock Therapy

Kaplan-Meyer curve for survival over the study duration according to ICD shock status is depicted in Figure 1B. For this purpose, patients were divided into 3 groups: no shock (n=199), inappropriate shock (n=70) and appropriate shock (n=47). When both appropriate and inappropriate shocks occurred, the patient was categorized as inappropriate shock. Thus the appropriate shock group included patients receiving only appropriate shocks. As shown in Figure 1B, no prognostic differences were observed between the groups of inappropriate shock and no shock (P=0.18). There was a lower trend in the survival rate in patients with appropriate shock compared with those with inappropriate shock (P=0.06). On the other hand, the survival rate was significantly different between the appropriate and no shock groups (P=0.002). Probability of death at 5 years was 29% in the appropriate shock group and 14% in the no shock group.

Proarrhythmic Consequences of Inappropriate ICD Therapy

The 70 patients who received at least 1 inappropriate shock did not have either syncope or proarrhythmia. In contrast, ATP induced proarrhythmia in 2 patients (0.6%) during sinus tachycardia (Figure 2), thereby calculated to be 0.18% of patients per year. This patient had first-degree and Wenckebach type atrioventricular block during sinus tachycardia. Some atrial events were included in the post-ventricular atrial refractory period, and ICD misrecognized Wenckebach type atrioventricular block as atrioventricular dissociation (Figure 2). When the tachycardia exceeded the VT detection rate, the atrial events in relation to ventricular-ventricular interval were unusual for sinus tachycardia because of prolonged atrioventricular interval (Figure 2). Therefore, ICD judged it as VT. Subsequent ATP induced VT that was terminated by high energy shock. However, these 2 patients did not have syncope because of inappropriate ATP therapy.

Effects of Period of ICD Implantation and Device Type

Because the morphology-based algorithm for detecting VT was used as a nominal setting after October 2006, we have divided the study population into 2 groups: before and after October 2006. Of the 316 patients, 233 (74%) were classified as the "recent" group. However, the cumulative event rate for first inappropriate shock was not significantly different between "old" and "recent" groups (Figure S1A). The major causes responsible for first inappropriate shock in each group were AF and sinus tachycardia, and there were no apparent time-dependent differences in this trend. The ratio of AF and sinus tachycardia was 48% and 26% in the "old" group and 42% and 44% in "recent" group, respectively.

In addition, the incidence of inappropriate shocks among patients with single-chamber (VVI) ICDs (n=75), dual-chamber (DDD) ICDs (n=91), and biventricular ICDs for cardiac resynchronization therapy (CRT) (n=67) in the "recent" group (n=233)

Table 3. Multivariate Analysis of Predictors of Inappropriate Shock

	HR	95% CI	P value
Age ≤56 years	1.68	1.02–2.77	0.043
Paroxysmal AF	3.00	1.69–5.31	0.0002
Stroke	2.23	1.11–4.47	0.024
No use of diuretics	1.71	1.02–2.93	0.039

CI, confidence interval; HR, hazard ratio. Other abbreviation as in Table 1.

Table 4. Characteristics of Subgroup of Patients With Paroxysmal AF

	No inappropriate shock (n=30)	Inappropriate shock (n=18)	P value
Age (years)	64±2	55±3	0.024
Male	24 (80)	12 (67)	0.302
LVEF (%)	37±3	41±4	0.324
LAD (mm)	50±1	46±2	0.071
NYHA class III–IV	16 (53)	6 (33)	0.237
Primary prevention	5 (17)	4 (22)	0.633
Device			0.139
Single chamber	2 (7)	1 (6)	
Dual chamber	14 (47)	12 (67)	
CRT	14 (47)	5 (28)	
Underlying heart disease			0.322
Ischemic	12 (40)	4 (22)	
Non-ischemic	16 (53)	11 (61)	
PED or CSA	2 (7)	3 (17)	
Medication			
β-blocker	24 (80)	15 (83)	0.775
Amiodarone	21 (70)	10 (56)	0.311
Ca^{2+} antagonists	4 (13)	6 (33)	0.099

Data are mean±SE or n (%). LAD, left atrial dimension. Other abbreviations as in Table 1.

Table 5. Multivariate Analysis of Predictors of Inappropriate Shock in Patients With Paroxysmal AF

	HR	95% CI	P value
Age ≤60 years	2.99	1.13–7.89	0.027
LAD ≤45 mm	0.92	0.26–3.29	0.902
Ca^{2+} antagonist	4.19	1.04–16.9	0.044

Abbreviations as in Tables 1,3,4.

was examined. As shown in the Kaplan-Meier curves for the occurrence of first inappropriate shock, the type of device did not produce significant effect on its incidence even in the "recent" group (Figure S1B).

Predictors of Inappropriate Shocks

In order to identify the predictors of inappropriate shocks, Cox proportional-hazards regression analysis was performed. Younger age (≤56 years old) (hazard ratio [HR] 1.52, 95% confidence interval [CI] 0.95–2.43, P=0.081), paroxysmal AF (HR 2.25, 95% CI 1.31–3.85, P=0.003), stroke (HR 1.79, 95% CI 0.91–3.49, P=0.090), no diuretics use (HR 1.48, 95% CI 0.91–2.43, P=0.113), and dyslipidemia (HR 0.70, 95% CI 0.41–1.17, P=0.172) were related to inappropriate shocks in terms of P value less than 0.2 by univariate analysis. Persistent AF (HR 1.02, 95% CI 0.47–2.23, P=0.969) did not increase the risk of inappropriate shocks. Multivariate analysis demonstrated that younger age (≤56 years old), paroxysmal AF, stroke, and no use of diuretics were predictors for inappropriate shocks (Table 3).

Subgroup of Patients With Paroxysmal AF and Their Predictors of Inappropriate Shocks

A total of 48 patients were diagnosed as having paroxysmal AF before ICD implantation; 18 of 48 patients (37.5%) received an inappropriate shock. The cause of inappropriate shock was AF in 17 patients except for sinus tachycardia in 1 patient. Patients with paroxysmal AF were subdivided in terms of presence or absence of inappropriate shock (Table 4). Those who experienced inappropriate shocks were significantly younger, although other characteristics such as NYHA functional class and type of device did not differ between groups. Multivariate analysis identified younger age (≤60 years old) and use of calcium antagonist as predictors for inappropriate shocks (Table 5).

Table 6. Summary of Arrhythmic Syncope in Relation to ICD Therapy in Previous Reports

	Bänsch et al[18]	Olatidoye et al[20]	Abello et al[19]
Total no. of ICD recipients	421	114	76
Mean or median follow-up (months)	26	35	33
No. of ICD recipients with arrhythmic syncope	57	18	9
Records obtainable	57	13	9
Cause of syncope			
VT/VF			
With appropriate therapy	47 (82.4)	8 (62)	6 (67)
Without appropriate therapy	1 (1.8)	0 (0)	0 (0)
Fast nonsustained VT	1 (1.8)	0 (0)	0 (0)
With proarrhythmic therapy*	6 (10.5)	4 (30)	2 (22)
Inappropriate therapy	2 (3.5)	1 (8)	1 (11)**

Data are n or n (%). *Appropriate antitachycardia pacing and/or low-energy shock resulted in acceleration of VT or induction of VF, thereby leading to loss of consciousness. **During AF, low-energy shock (≤5 J) induced VF. VT/VF, ventricular tachycardia or ventricular fibrillation. Other abbreviation as in Table 1.

Discussion

The present study is the first to demonstrate that the annual rate of proarrhythmic inappropriate ICD therapy (shock and ATP) was 0.18% of ICD recipients during the mean follow-up of 43 months, and that it was induced only by ATP. Inappropriate ICD therapy did not induce syncope. Paroxysmal AF, stroke, younger age (≤56 years old), and no use of diuretics were identified as the independent predictors for inappropriate ICD shocks.

When a patient receives ICD therapy, it restricts driving a vehicle because the recurrence rate of appropriate ICD therapy is high and could be associated with syncope.[10,14,15] Although ICD implantation can reduce the incidence of syncope,[16,17] a previous study reported that it was 10% at 1 year, and approximately 20% at 3 years in 421 ICD recipients.[18] In other previous studies, the incidence of syncope was reported to be approximately 10% in generalized ICD patients[6,8,15–20] and the major etiology was arrhythmic syncope except in 1 study.[16] Two recent clinical trials (MADIT-RIT[8] and ADVANCE III trial,[6] mainly registering ICD patients for primary prevention) reported the incidence of syncope as <5%.

Detailed analysis of arrhythmic syncope in 3 studies is given in Table 6.[18–20] Most patients presented with syncope during VT or VF, and some of them were induced by proarrhythmic ICD therapy, especially by ATP or low-energy shock. On the other hand, a small proportion of the patients presented with syncope from inappropriate therapy, but details were not available except for 1 patient,[19] who had syncope caused by VF induced by an inappropriate low-energy shock (≤5 J) during AF. Based on these data, the annual rate of syncope associated with inappropriate ICD therapy was calculated to be 0.22%,[18] 0.30%[20] and 0.48%.[19] However, there is a paucity of studies investigating the mechanisms of syncope induced by inappropriate ICD therapy.

The annual incidence of proarrhythmic inappropriate ICD therapy was 0.18% in our study, which appears to be lower than reported in the previous studies (0.22–0.48%), probably because of the use in our study of ICD devices equipped with non-committed mode[21] after 1991 (ie, third-generation ICD) and the high initial shock energy (10 J) for the VT zone prevented proarrhythmic VT/VF induced by low-energy shock (≤5 J).[2,22] In fact, inappropriate ICD shocks did not lead to proarrhythmia or syncope in our study patients.

Recently, the interim analysis of the Nippon Storm Study demonstrated that approximately 80% of recurrent inappropriate ICD therapy occurred within 180 days from first inappropriate therapy.[23] In addition, the annual rate of proarrhythmic inappropriate therapy of 0.18% was lower than that (0.73%) reported as the Japanese annual traffic accident rate in 2013.[24] However, a 12-month restriction is obligatory following ICD therapy (including shocks and ATP), irrespective of appropriateness, in Japan.[14,25] The 1-year driving restriction after inappropriate ICD therapy in Japan could be reduced in the era of modern ICD devices.

In the present study, we identified several independent predictors for inappropriate shocks, including younger age, paroxysmal AF, stroke, and no use of diuretics. As with our study, the previous studies showed that being younger independently predicted the occurrence of inappropriate ICD therapy,[26,27] probably because these patients have high levels of physical activity in their daily lives and so their heart rate could reach the detection zone of VT/VF more easily.

Several studies found prior AF was the major reason[28] and the independent predictor of inappropriate ICD therapy.[4,26,27,29–31] Because AF was one of the major reasons for inappropriate shocks in our study (Figure 1C), it is natural that a history of AF is its predictor. However, the type of AF has not been determined.[4,26,27,29–31] Multivariate analysis of our study data demonstrated that the presence of paroxysmal, but not persistent, AF carried a 3-fold increase in the risk of inappropriate ICD shocks (Table 3). The reason for no risk of inappropriate shocks in patients with persistent AF could be that they had received optimal rate control therapy compared with those with paroxysmal AF.

Stroke and no use of diuretics are novel independent predictors for inappropriate shocks. Patients with post-ischemic stroke have been shown to have prolongation of the QT interval,[32] frequent occurrence of tachycardia and bradycardia,[33] and impaired heart rate variability.[34] These manifestations are thought to be triggered by autonomic dysfunction after stroke,[34,35] which may adversely facilitate inappropriate ICD therapy. We speculate that physical activity in patients without diuretic therapy was higher than in those with diuretic therapy, thereby exaggerating the rate of sinus tachycardia as well as AF. Therefore, patients without diuretic use might be prone to inappropriate shocks.

The subgroup analysis regarding ICD patients with AF showed that the use of a calcium antagonist was significantly related to the incidence of inappropriate ICD shock based on

multivariate analysis. This appears to be contradictory, because calcium antagonists are generally used for rate control of AF in most patients. We speculate there are 2 reasons for this. First, the patients taking a calcium antagonist might have been prescribed that therapy because of frequent attacks of paroxysmal AF, hence they were prone to having inappropriate shocks. However, data concerning the frequency of paroxysmal AF before ICD implantation were not available in the present study. Second, calcium antagonists included not only non-dihydropylidine but also dihydropylidine. The dihydropylidine calcium antagonists may have activated the sympathetic nervous system, thereby leading to increased heart rate and inducing inappropriate ICD shocks.

Study Limitations

First, this was a retrospective study conducted in a single center, so the findings need to be confirmed in a multicenter study before they can be generalized. Second, the device programming and types of device were determined by the attending electrophysiological specialist based on patient background such as ICD indication (ie, primary or secondary prevention[36]) and heart failure status, which might affect the incidence of inappropriate ICD therapy. In fact, recent ICD programming with higher detection rate and/or longer detection interval reduces the incidence of inappropriate ICD therapy up to approximately 5%,[6,8,9] which was lower than the 7.6–44% in previous reports.[4,10,23,26,27,29–31] It is controversial whether dual-chamber ICD devices decrease the level of inappropriate ICD therapy compared with single-chamber devices.[37–39] However, a subanalysis of MADIT-CRT reported a trend (P=0.09) toward a decrease in inappropriate shocks with dual-chamber ICDs compared with single-chamber ICDs.[37]

Conclusions

The annual rate of proarrhythmic ICD therapy was 0.18%. Young age, paroxysmal AF, stroke, and no use of diuretics were identified as predictors for inappropriate ICD shocks.

Acknowledgments

We thank Dr Masayuki Sakurai, Director of Hokko Memorial Hospital, for constant encouragement of this study.

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Supplementary Files

Supplementary File 1

Figure S1. Cumulative event rate for first inappropriate shock comparing period of ICD implantation and device type.

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-15-0306