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Current Status of Primary Prevention of Sudden Cardiac Death With Implantable Cardioverter Defibrillator in Patients With Chronic Heart Failure

– A Report From the CHART-2 Study –

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Background: The current status of primary prevention of sudden cardiac death (SCD) with implantable cardioverter defibrillator (ICD) in patients with heart failure with reduced ejection fraction remains to be fully elucidated in Japan.

Methods and Results: In the chronic heart failure (CHF) cohort study, the CHART-2 Study, we enrolled 2,778 consecutive patients with NYHA class II–III. According to the Japanese Circulation Society guideline of prophylactic ICD, we divided them into 3 groups: group A, class I indication; B, class IIa; and C, no indication. During the (median) 3.2-year follow-up, 79 fatal arrhythmic events (FAE), defined as composite of sudden cardiac/arrhythmic death, ventricular tachycardia/fibrillation and appropriate ICD therapy, occurred. In the groups A, B and C, the prevalence of FAE was 16.1%, 8.9% and 1.9%, respectively; the use of prophylactic ICD among those with FAE, however, was only 44%, 9% and 6%, respectively. In the groups A and B combined, chronic atrial fibrillation (cAF) and left ventricular end-diastolic dimension (LVDd) ≥65 mm were independent predictors of FAE, and, when combined, their prognostic impact was highly significant (hazard ratio, 7.01; P<0.001).

Conclusions: Primary prevention of SCD with ICD in CHF patients is validated but is still underused in Japan, and the combination of cAF and LVDd ≥65 mm may be a useful indication of prophylactic ICD implantation. (*Circ J* 2015; **79:** 381–390)

Key Words: Heart failure; Implantable cardioverter defibrillator; Sudden cardiac death

Implantable cardioverter defibrillator (ICD) is the established therapy for fatal ventricular tachyarrhythmia.[1–3] Previous randomized controlled trials have demonstrated the efficacy of prophylactic ICD implantation in patients with heart failure (HF) with reduced left ventricular ejection fraction (HFrEF) due to ischemic heart disease (IHD) and non-ischemic dilated cardiomyopathy (NIDCM), such as the Multicenter Automatic Defibrillator Implantation Trial-II (MADIT-II)[4] and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT).[5] These findings have been incorporated into the American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guidelines for primary prevention of sudden cardiac death (SCD).[2,6] In Japan, however, no large clinical trial has been conducted to examine the benefit of ICD for primary prevention of SCD. Consequently, the current guidelines of the Japanese Circulation Society (JCS) for prophylactic ICD implantation in patients with HFrEF[3] are based on the randomized controlled trials conducted in Western countries (**Table 1**).[4,5,7–10] Furthermore, it is conceivable that the prevalence of SCD in Japanese HFrEF patients is not so high as compared with Caucasian patients.[11,12] Indeed, the efficacy of prophylactic ICD implantation to prevent SCD remains to be fully elucidated in Japanese chronic HF (CHF) patients. In the present study, the aim was thus to elucidate the current status of primary prevention of SCD with ICD in HFrEF patients in our CHF registry, the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) study.[13–16]

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Table 1. Guidelines for Primary Prevention of SCD With ICD

ACC/AHA (2012)[1,6]		
MI	Class I	LVEF ≤40% NSVT, Positive EPS
		LVEF ≤35% NYHA II–III
		LVEF ≤30% NYHA I
NIDCM	Class I	LVEF ≤35% NYHA II–III
ESC (2006)[2]		
MI	Class I	LVEF ≤30–40% NYHA II–III
NIDCM	Class I	LVEF ≤30–35% NYHA II–III
JCS (2011)[3]		
Structural heart disease (IHD or NIDCM)	Class I	LVEF ≤35%, NYHA II–III, NSVT
		LVEF ≤35%, NYHA I, NSVT, Positive EPS
	Class IIa	LVEF ≤35%, NYHA II–III

ACC/AHA, American College of Cardiology/American Heart Association; ESC, European Society of Cardiology; EPS, electrophysiological study; IHD, ischemic heart disease; JCS, Japanese Circulation Society; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NIDCM, non-ischemic dilated cardiomyopathy; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; SCD, sudden cardiac death.

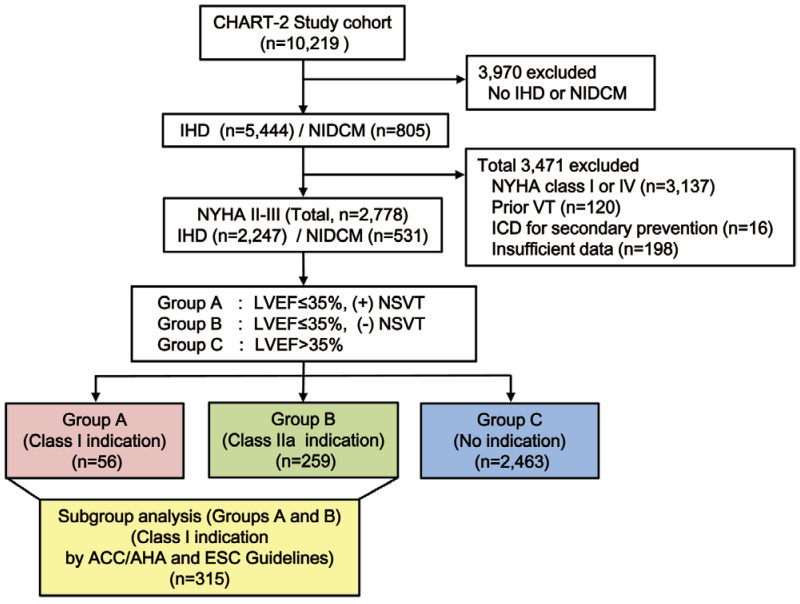

Figure 1. Study flow diagram. IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; NIDCM, non-ischemic dilated cardiomyopathy; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; VT, ventricular tachycardia.

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Methods

Subjects and Inclusion Criteria

The CHART-2 study is a multicenter, prospective observational cohort study, in which 10,219 eligible patients were aged ≥20 years with significant coronary artery disease or in HF stages B, C and D, as defined by the ACC/AHA guidelines for the diagnosis and management of HF.[17] The study was started in October 2006 and patient enrollment was successfully ended in March 2010 with 10,219 patients registered from the 24 participating hospitals. The details of the design, purpose and clinical characteristics of the patients have been previously reported in detail (NCT00418041).[13–16] The CHART-2 study was approved by the local ethics committee in each participating hospital and informed consent was obtained from all patients. In the CHART-2 study, left ventricular ejection fraction (LVEF) was evaluated on echocardiography once per year. The LVEF data at enrollment were used in the present study regardless of ICD or cardiac resynchronization therapy with defibrillator (CRT-D) implantation date. Non-sustained ventricular tachycardia (NSVT) was defined as ≥3 consecutive ventricular premature beats but terminated spontaneously within 30 s,[18] and NSVT data were obtained on 24-h Holter electrocardiogram (ECG) or prior clinical records at enrollment. In the present study, we enrolled consecutive IHD or NIDCM patients with symptomatic HF (New York Heart Association [NYHA] class II–III; Figure 1). We excluded HF patients in NYHA class I or IV, those with a prior history of ventricular tachycardia or ventricular fibrillation (VT/VF), those with implanted ICD for secondary prevention, and those without NYHA class or LVEF data (Figure 1). Finally, a total of 2,778 HF patients with IHD

Table 2. Baseline Patient Characteristics

	All patients (n=2,778)	Group A (n=56)	Group B (n=259)	Group C (n=2,463)	P-value
Age (years)	69.8±11.3	66.5±11.1	66.4±12.8	70.3±11.1	<0.001
Men	74.2	87.7	77.2	73.6	0.007
CAD	80.9	45.6	59.1	84.0	<0.001
NIDCM	19.1	54.4	40.9	16.0	<0.001
Comorbidity					
HT	85.8	73.8	76.4	87.0	<0.001
DM	37.2	33.3	37.1	37.3	0.868
HL	82.5	78.9	81.9	82.7	0.106
pAF	7.8	19.6	5.8	8.8	0.004
cAF	18.6	33.9	19.3	18.2	0.011
NSVT	16.3	100	0	4.8	<0.001
Clinical status					
NYHA class II	90	70.2	83.4	91.1	<0.001
NYHA class III	10.1	29.8	16.6	8.9	<0.001
BMI (kg/m^2)	23.7±4.4	23.4±4.3	22.4±4.2	23.8±4.4	<0.001
SBP (mmHg)	127±19	111±17	116±17	128±18	<0.001
DBP (mmHg)	71±11	65±11	68±11	73±11	<0.001
HR (beats/min)	71±14	71±13	74±14	71±14	0.0068
Measurements					
LVDd (mm)	52.7±9.0	68.0±7.7	63.6±9.0	51.2±7.9	<0.001
LAD (mm)	41.3±8.3	47.2±8.9	43.3±9.4	40.9±8.1	<0.001
LVEF (%)	55.8±15.3	27.4±4.9	28.6±5.3	59.3±12.4	<0.001
Hb (g/dl)	13.3±2.1	13.7±2.2	13.2±2.8	13.3±2.1	0.233
BUN (mg/dl)	19.5±9.7	24.0±11.0	23.0±14.0	19.0±9.0	<0.001
Cr (mg/dl)	1.0±0.8	1.2±0.5	1.3±1.3	1.1±0.9	<0.001
eGFR (ml·min^{-1}·1.73 m^{-2})	59.3±20.5	52.1±19.8	57.2±22.9	60.9±20.7	<0.001
BNP (pg/ml) [IQR]	89 [37–216]	218 [135–561]	242 [116–502]	77 [34–181]	<0.001
Medications					
β-blockers	52.3	87.8	69.1	49.7	<0.001
RASI	70	84.2	83	68.3	<0.001
Loop diuretics	41.5	87.7	74.9	37.0	<0.001
Aldosterone inhibitor	18.4	61.4	43.2	14.8	<0.001
Statins	49.3	38.6	40.1	50.4	0.002
Amiodarone	2.2	35.1	3.4	1.3	<0.001
ICD for primary prevention					
Total	55 (2.0)	17 (30.4)	17 (6.6)	21 (0.9)	<0.001
Implanted before enrollment	7 (0.3)	4 (7.1)	1 (0.4)	2 (0.08)	<0.001
Implanted after enrollment	48 (1.7)	13 (23.2)	16 (6.2)	19 (0.8)	<0.001
CRT-D	51 (92.7)	15 (88.2)	17 (100)	19 (90.5)	0.368

Data given as mean±SD, % or n (%). BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CAD, coronary artery disease; cAF, chronic atrial fibrillation; Cr, serum creatinine; CRT-D, cardiac resynchronization therapy with defibrillator; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HL, hyperlipidemia; HR, heart rate; HT, hypertension; ICD, implantable cardioverter defibrillator; LAD, left atrial diameter; LVDd, left ventricular end-diastolic diameter; pAF, paroxysmal atrial fibrillation; RASI, rennin-angiotensin system inhibitor; SBP, systolic blood pressure. Other abbreviations as in Table 1.

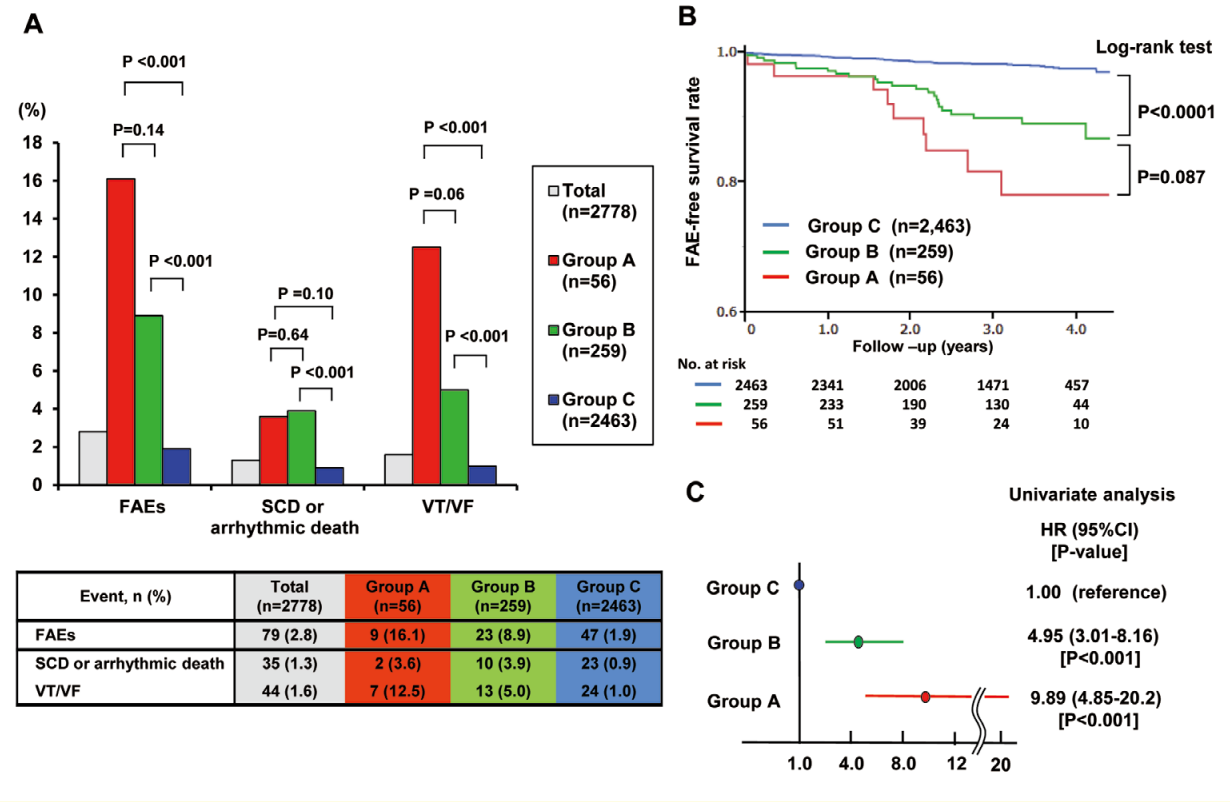
(n=2,247) or NIDCM (n=531) were included in the present study (Figure 1).

Outcomes

We evaluated outcome with regard to fatal arrhythmic events (FAE), which were defined as the composite of SCD or arrhythmic death, VT/VF and appropriate ICD therapy.[18–20] SCD was defined as instantaneous, unexpected death or death within 1 h of symptom onset not related to circulatory failure; arrhythmic death as death from VT/VF; VT as tachycardia lasting >30 s or unstable hemodynamic tachycardia; VF as a polymorphic ventricular tachyarrhythmia with RR interval <200 ms; and appropriate ICD therapy as ICD shock or anti-tachycardia pacing for VT/VF. We counted the number of VT/VF events including appropriate ICD therapy.

Statistical Analysis

To evaluate the current status of prophylactic ICD in IHD or NIDCM patients with CHF, we divided the 2,778 patients into the following 3 groups based on the JCS guideline:[3] group A, LVEF ≤35% with NSVT (JCS class I indication, n=56); group B, LVEF ≤35% without NSVT (JCS class IIa indication, n=259);



Event, n (%)	Total (n=2778)	Group A (n=56)	Group B (n=259)	Group C (n=2463)
FAEs	79 (2.8)	9 (16.1)	23 (8.9)	47 (1.9)
SCD or arrhythmic death	35 (1.3)	2 (3.6)	10 (3.9)	23 (0.9)
VT/VF	44 (1.6)	7 (12.5)	13 (5.0)	24 (1.0)

Figure 2. (**A**) Prevalence of fatal arrhythmic events (FAE), sudden cardiac death (SCD) and arrhythmic death, and ventricular tachycardia or fibrillation (VT/VF; including appropriate implantable cardioverter defibrillator therapy) in group A (left ventricular ejection fraction [LVEF] ≤35% with non-sustained ventricular tachycardia [NSVT]), group B (LVEF ≤35%, without NSVT), and group C (LVEF >35%). (**B**) Kaplan-Meier curves for FAE. (**C**) Relative hazard ratio (HR) for FAE in group A and B as compared with group C. CI, confidence interval.

and group C, LVEF >35% (others except class I and IIa, n=2,463; Figure 1). Comparison of data among the 3 groups was performed using analysis of variance (ANOVA) for continuous variables and Fisher's exact test for categorical variables. Continuous variables are described as mean±SD. The differences in the prevalence of FAE among the 3 groups were evaluated using Fisher's exact test. Kaplan-Meier curves were plotted to evaluate the association among the 3 groups and FAE. Relative risk for FAE in groups A and B compared with group C was examined using univariate Cox proportional hazard modeling. In addition, to further examine the predictors of FAE, we performed subgroup analysis in group A and B patients (n=315; Figure 1).[3] We divided them into FAE (n=32) and non-FAE groups (n=283). The predictors of FAE were examined on univariate and multivariate Cox proportional hazard modeling. The covariates for multivariate analysis (stepwise method) included age, sex, body mass index, left ventricular end-diastolic diameter (LVDd), left atrial diameter, LVEF, paroxysmal atrial fibrillation (pAF), chronic AF (cAF), serum brain natriuretic peptide (BNP), estimated glomerular filtration rate (eGFR), β-blocker, renin-angiotensin system inhibitors, aldosterone antagonists, loop diuretics and amiodarone. We also performed Kaplan-Meier and relative hazard analysis in the subgroup using the same methods as for the aforementioned full model. All statistical analysis was done using SPSS Statistics 20.0 (SPSS, Chicago, IL, USA) and statistical significance was defined at P<0.05.

Results

Clinical Characteristics

Clinical characteristics of the 2,778 CHF patients are listed in Table 2. The mean age was 69.8±11.3 years and 2,060 (74.2%) were male. IHD and NIDCM patients accounted for 80.9% and 19.1%, respectively. groups A and B were younger than group C. Concerning the prevalence of underlying diseases, that of coronary artery disease was higher in group C and that of pAF and cAF was higher in group A. The prevalence of NYHA class Ⅲ increased in the order of group A, B and C. LVDd was the largest in group A, followed by group B and then group C. LVEF and eGFR were lower and BNP was higher in groups A and B than in group C. Medications, except for statins, were used more frequently in groups A and B than in group C.

Prevalence of FAE

During the median follow-up of 3.2 years, there were 79 FAE, including 9 in group A (2 SCD and 7 VT/VF), 23 in group B (10 SCD and 13 VT/VF), and 47 in group C (23 SCD and 24 VT/VF), and the prevalence of FAE was significantly higher in groups A and B than in group C (Figure 2A). FAE-free survival rate was significantly lower in groups A and B than in group C and tended to be lower in group A than in group B

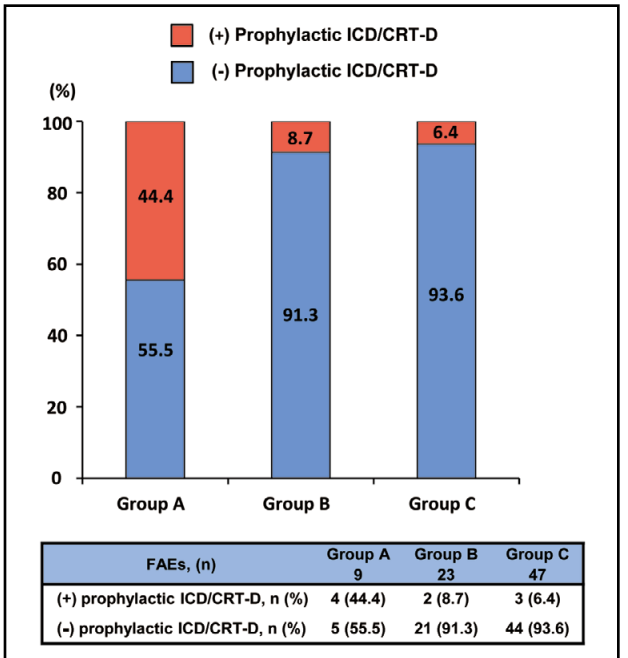
(Figure 2B). As compared with group C, the hazard ratios (HR) for groups A and B were 9.89 (95% confidence interval [CI]: 4.82–20.2) and 4.95 (95% CI: 3.01–8.16), respectively, and both were significantly high (both P<0.0001; Figure 2C).

Prevalence of FAE in ICD/CRT-D

We collected the data of FAE and implantation of prophylactic ICD or CRT-D from enrollment to March 2011, and counted the number of VT/VF events including appropriate ICD therapy. The proportion of patients with prophylactic ICD implantation in groups A, B, and C was 30.4%, 6.6%, and 0.9%, respectively, who met class I, IIa, and others according to the JSC guidelines for CHF patients with LV dysfunction (Table 2). In the patients who had FAE, the proportion of patients with prophylactic ICD implantation in groups A, B, and C was only 44.4% (4 of 9), 8.7% (2 of 23) and 6.4% (3 of 47), respectively (Figure 3).

Risk Stratification of FAE

We performed subgroup analysis in group A and B patients (n=315) to further stratify FAE risk. We divided them into 2 groups: FAE (n=32) and non-FAE (n=283). The baseline characteristics of the FAE and non-FAE groups are given in Table 3. The FAE group was characterized by higher prevalence of cAF (P=0.03) and more enlarged LVDd (P<0.0001) than the non-FAE group. There were no other significant differences between the 2 groups. Table 4 lists univariate and multivariate Cox proportional hazards modeling for 315 patients. On multivariate Cox proportional analysis, cAF and LVDd ≥65 mm were significant and independent predictors of FAE (cAF: HR, 2.88; 95% CI: 1.41–5.89, P=0.004; LVDd ≥65 mm: HR, 2.30; 95% CI: 1.10–4.80, P=0.026). We divided 308 patients with available LVDd data in group A and B (n=315) into the following 4 groups in order to examine the prevalence of FAE: (1) cAF not present and LVDd <65 mm; (2) LVDd ≥65 mm alone; (3) cAF alone; and (4) LVDd ≥65 mm and cAF. The prevalence of FAE in the 4 groups was 4.4% (6/135), 12.3% (13/106), 12.8% (5/39) and 28.6% (8/28), respectively (Figure 4A). Figure 4B shows the Kaplan-Meier analysis of the 4 groups, with group C as a reference. The FAE-free survival rate was significantly lower in the group with cAF and LVDd ≥65 mm than in other 3 groups, and that in the groups with LVDd ≥65 mm alone and with cAF alone was also significantly lower compared with the group without cAF or LVDd ≥65 mm (Figure 4B). Figure 4C shows the relative HR (95% CI, P-value) for FAE in the 308 patients. Relative HR for the groups with LVDd ≥65 mm alone, cAF alone, or cAF plus LVDd ≥65 mm was significantly higher compared with the group without cAF or LVDd ≥65 mm: 2.89 (1.10–7.61, P=0.032), 3.37 (1.03–11.1, P=0.045) and 7.01 (2.43–20.2, P<0.001), respectively (Figure 4C).



FAEs, (n)	Group A 9	Group B 23	Group C 47
(+) prophylactic ICD/CRT-D, n (%)	4 (44.4)	2 (8.7)	3 (6.4)
(-) prophylactic ICD/CRT-D, n (%)	5 (55.5)	21 (91.3)	44 (93.6)

Figure 3. Prevalence of fatal arrhythmic events (FAE) in treated or untreated patients with prophylactic implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy with defibrillator (CRT-D). Group A, left ventricular ejection fraction (LVEF) ≤35% with non-sustained ventricular tachycardia (NSVT); group B, LVEF ≤35%, without NSVT; and group C, LVEF >35%.

Discussion

The major findings of the present study are that (1) the JCS guideline for prophylactic ICD implantation in patients with HFrEF[3] is validated in real-world clinical practice in Japan; (2) the prophylactic use of ICD, however, is still low in Japan; and (3) the combined risk stratification of cAF and LVDd ≥65 mm could be a useful predictor of FAE in Japanese patients with class I/IIa JCS indication of prophylactic ICD.[3]

Prevalence of FAE in Patients Meeting the JCS Criteria

The importance of prophylactic ICD implantation for symptomatic HFrEF has been established based on the previous clinical studies.[4,5,7–10] In patients with IHD and HFrEF, MADIT-I (LVEF ≤35%, NSVT and positive electrophysiological study [EPS])[21] and MADIT-II (LVEF ≤30%)[4] showed that prophylactic ICD therapy reduced cardiac mortality compared with conventional therapy. SCD-HeFT with IHD and NIDCM patients with NYHA class II/III and LVEF ≤35% also showed that ICD therapy reduced cardiac death to 23%.[5] There have been no large-scale data available in Japan regarding prophylactic ICD therapy and thus the indication for primary prevention with ICD for HFrEF patients has been based on these Western trials.[4,5,7–10]

There are several reports of SCD rate in patients with reduced LV function in Japan. Tanno et al reported that the prevalence of SCD was only 1.2% in Japanese patients meeting the MADIT-II criteria during a mean 30-month follow-up.[11] The Heart Institute of Japan Acute Myocardial Infarction (HIJAMI-II) trial also showed that the prevalence of SCD in patients meeting the MADIT-II criteria was 5.1% in 5 years in Japan.[12] In contrast, we have previously reported that 3-year prevalence of SCD in CHF patients with LVEF <30% was 15% in the CHART-1 study.[22] In the present CHART-2 study, the prevalence of SCD and arrhythmic death in HFrEF patients with LVEF <30% during a mean 2.7-year follow-up was markedly improved to 4.9% (9 in 185 IHD and NIDCM patients), coming close to that in the aforementioned Japanese studies. This improvement can be attributed to the progress in CHF management in Japan. Previous studies reported that the use of β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists significantly reduced the risk of cardiovascular death and SCD in CHF patients.[23–26] Indeed, these medications in patients with DCM were more frequently used in the CHART-2 compared with

Table 3. Baseline Characteristics vs. Presence of FAE

	All patients (n=315)	FAE (n=32)	Non-FAE (n=282)	P-value
Age (years)	66.5±12.4	68.9±10.3	66.3±12.6	0.25
Men	79	78.1	79.2	0.89
Comorbidity				
HT	75.8	81.3	72.3	0.45
DM	36.5	37.5	36.4	0.90
HL	81.2	84.4	80.9	0.63
pAF	8.3	6.3	8.5	0.49
cAF	30.5	46.9	28.3	0.01
CAD	56.8	62.5	56.2	0.49
NSVT	17.8	28.1	16.6	0.10
Clinical status				
NYHA class II	80.9	81.2	80.9	0.96
NYHA class III	19.0	18.8	19.1	0.97
SBP (mmHg)	115±17.3	117±19.2	115±17.1	0.56
DBP (mmHg)	67.8±11.2	68.8±11.6	68.4±11.0	0.57
HR (beats/min)	73.2±13.7	74.6±13.8	73.0±13.8	0.55
Measurements				
LVDd (mm)	64.3±8.9	70.4±10.9	63.6±8.4	<0.0001
LAD (mm)	43.9±9.4	47.0±11.4	43.6±9.2	0.06
LVEF (%)	28.4±5.3	27.8±5.2	28.4±5.3	0.51
Hb (g/dl)	13.3±2.6	13.6±1.8	13.3±2.7	0.55
eGFR ($ml \cdot min^{-1} \cdot 1.73 m^{-2}$)	51.8±20.7	49.3±16.6	52.2±21.2	0.61
BNP (pg/ml) [IQR]	237 [124–514]	301 [157–452]	242 [116–502]	0.65
Medications				
β-blockers	72.4	78.1	71.7	0.54
RASI	83.2	81.3	83.4	0.80
Loop diuretics	77.1	90.6	75.6	0.07
Aldosterone inhibitor	46.3	62.5	44.5	0.06
Statins	40.0	50.0	38.9	0.26
Amiodarone	8.9	6.3	9.2	0.75

Data given as mean±SD, % or n (%). FAE, fatal arrhythmic event. Other abbreviations as in Table 2.

the CHART-1 study.[27]

The prevalence of SCD in HFrEF in Western patients tends to be higher compared with Japanese patients. In MADIT-II, the SCD rate was 10.0% in the conventional therapy group during a mean 20-month follow-up.[28] SCD-HeFT noted an SCD prevalence of 11.2% during a mean 3.7-year follow-up.[5] The 3-year probability of SCD was 15.5% for myocardial infarction patients with reduced LVEF ≤30% in the TRACE study.[29] In VALIANT, it was 10.4% during a median 24.7-month follow-up in myocardial infarction patients with LVEF ≤30%.[30] The difference in SCD rate in HFrEF patients between Japanese and Western populations has been incorporated into the JCS guideline for prophylactic ICD implantation in NYHA II/III CHF patients. In the JCS guidelines, patients with both NSVT and LVEF ≤35% and those with LVEF ≤35% alone are classified as I and IIa indications, respectively,[3] whereas the presence of NSVT is not mandatory for class I indication in the ACC/AHA and ESC guidelines (Table 1).[2,6]

In the present study, the prevalence of SCD and arrhythmic death during the 3-year follow-up was similar between group A (JCS class I) and B (JCS class IIa), although it was higher in both groups compared with group C. The FAE-free survival rate, however, was significantly higher in group C than in group A or B and tended to be lower in group A than in group B. These results suggest that the current JCS guidelines for HFrEF patients can stratify the risk of FAE in Japanese patients.

Underuse of ICD in Japan

Patients eligible for prophylactic ICD implantation do not always undergo the therapy in real-world practice and some patients eligible for ICD could have FAE before ICD therapy. It has been reported that the use of prophylactic ICD implantation was low in clinical practice, even in Western countries.[31,32] Hoang et al reported that the utilization rate of ICD was 38% among patients with class I indication in USA.[31] Parkash et al reported that only 16% of patients eligible for a primary prevention ICD were referred in a community-based cohort study in Canada, whereas a significant mortality benefit was noted for ICD implantation.[32] In the present study, the implantation rate of ICD/CRT-D was also low: 30% in group A (LVEF ≤35% and NSVT), 6.6% in group B (LVEF ≤35% but no NSVT), and in total 10.8% in groups A and B. Furthermore, the proportion of patients with prophylactic ICD/CRT-D implantation among those who had FAE was also low: 44% in group A and 9% in group B (Figure 3), indicating that a considerable number of patients did not have ICD implantation despite the positive indication.

There are several reports regarding the factors influencing

Table 4. Significant Predictors of FAE

	HR	95% CI	P-value
Univariate analysis			
Age	1.02	0.99–1.02	0.81
Sex	0.89	2.82–6.79	0.23
BMI	0.92	1.91–3.88	0.18
SBP	1.01	0.98–1.03	0.37
pAF	0.76	0.18–3.17	0.70
cAF	2.76	1.36–5.60	0.005
NSVT	1.94	0.89–4.12	0.09
LVDd ≥65 mm	2.51	1.21–5.21	0.013
LAD >45 mm	1.60	0.76–3.37	0.22
LVEF	0.97	0.91–1.04	0.38
BNP	1.00	0.99–1.00	0.74
eGFR <60	1.32	0.64–2.74	0.46
β-blocker	0.85	0.32–2.26	0.75
RASI	0.68	0.26–1.77	0.43
Aldosterone antagonist	0.65	0.28–1.42	0.28
Loop diuretics	2.02	0.56–7.20	0.26
Amiodarone	0.43	0.37–9.33	0.07
Multivariate analysis			
cAF	2.88	1.41–5.89	0.004
LVDd ≥65 mm	2.30	1.10–4.80	0.026

LVDd and LAD given as median. The covariates for multivariate analysis (stepwise method) included age, sex, BMI, LVDd, LAD, pAF, cAF, BNP, eGFR, β-blocker, RASI, aldosterone antagonists, loop diuretics and amiodarone. CI, confidence interval; HR, hazard ratio. Other abbreviations as in Tables 1,2,4.

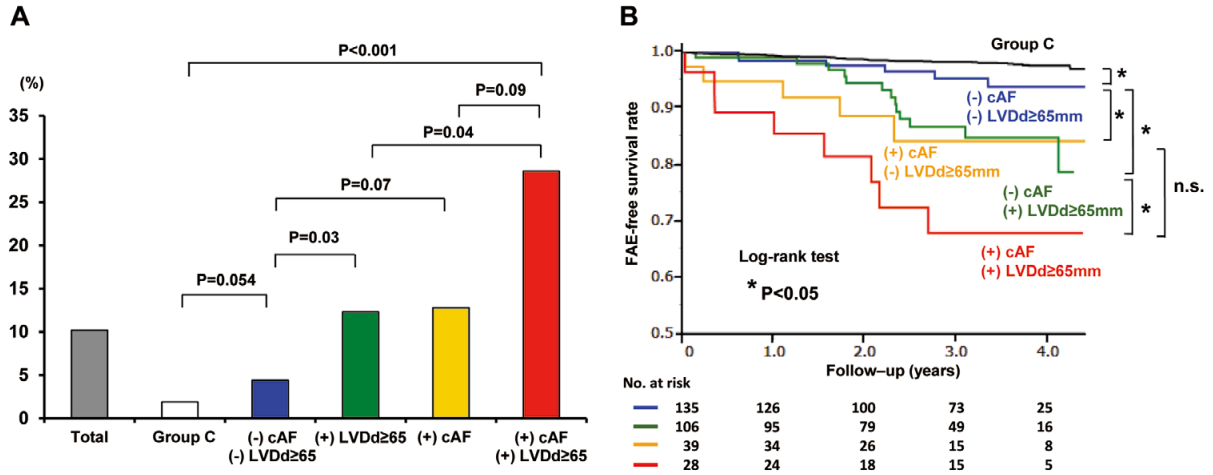
prophylactic ICD implantation in Western countries, although there are no reports available in Japan. It was reported that sex and race are significant influencing factors on ICD therapy among HF patients in the USA, with lower implantation rates in women and black patients compared with white male patients.[33] It was found in the USA that screening tools that queried LVEF and prior referral to an electrophysiolgist significantly increased the use of prophylactic ICD implantation.[34] These reports imply that the appropriate evaluation of patient condition may facilitate the appropriate use of prophylactic ICD implantation. It was also found in Canada and USA that sex, age, hospital teaching status, hospital size and history of HF were positive predictors of ICD implantation, while age, renal failure, liver failure and cancer were negative predictors for receiving an ICD.[35] Sadarmin et al showed that failure to refer from general physician to cardiologist and from cardiologist to electrocardiologist is the primary reason for the underuse of prophylactic ICD among eligible patients in the UK.[36] In the present study, only 1.6% (5/315) of patients eligible for ICD prophylactic implantation (group A and B) had undergone ICD implantation before enrollment. Furthermore, only 9.2% of that group of patients underwent ICD therapy after enrollment during a mean follow-up of 3.2 years (Table 1). Both reasons for the underuse of ICD prophylactic implantation could also be recognized in Japan.

Predictors for FAE in Patients Eligible for Prophylactic ICD

The previous studies have repeatedly demonstrated that LVEF is a strong predictor of SCD in IHD and NIDCM patients,[4,5,7–10] which has been incorporated into the ICD implantation criteria in all the ESC, AHA/ACC and JCS guidelines.[1–3] LVEF, however, was not an independent predictor of FAE in the present study. We consider that this is because we enrolled patients with severe reduced LVEF alone in the present study. In contrast, low LVEF alone may not be sufficient for SCD risk stratification because low LVEF includes the risk of both arrhythmic and non-arrhythmic death.[37] In the present study cAF and LVDd ≥65 mm were identified as independent predictors of FAE, having similar relative HR in HFrEF patients (groups A and B).

The relationship between SCD/FAE and AF has been reported.[38,39] Borleffs et al reported that patients with permanent AF, as compared with those without it, had a 1.7-fold risk of all-cause mortality and 2-fold risk of appropriate ICD shock during a mean 833-day follow-up after ICD implantation.[38] Similarly, the present study found that cAF was associated with a 2.9-fold increase in relative HR of FAE, defined as a composite of SCD, arrhythmic death, VT/VF and appropriate ICD therapy in group A and B patients. LV enlargement has also been reported to be a predictor of SCD in CHF, IHD with HFrEF and NIDCM patients.[40,41] It was reported that the combination of LVDd >70 mm and NSVT on Holter ECG was an independent arrhythmia risk predictor in German patients with idiopathic DCM.[40] We also reported that LVDd >60 mm was one of the independent risk markers of SCD in CHF patients in the CHART-1 study.[41] In contrast, in the present CHART-2 study, LVDd >65 mm, but not LVDd >60 mm, was a significant risk factor on univariate and multivariate Cox hazard analysis. We consider that the difference between the CHART-1 and CHART-2 studies is due to the difference in the patients studied. The CHART-1 study included patients with both preserved and reduced LV function, with mean LVDd 57±10 mm, which was smaller than that in the present subgroup in the CHART-2 study with LVEF ≤35%.

The combination of several factors may be helpful for further risk stratification for ICD implantation. MADIT-II investigators reported that ICD benefit was noted in patients with intermediate risk, with 1–4 of the 5 risk factors (NYHA class >II, age >70 years, blood urea nitrogen >26 mg/dl, QRS duration



	FAEs, (n)	Patients, (n)	Prevalence, (%)
Group C	47	2463	1.9
Total (Groups A/B)	32	308	10.2
(-) cAF, (-) LVDd≥65mm	6	135	4.4
(-) cAF, (+) LVDd≥65mm	13	106	12.3
(+) cAF, (-) LVDd≥65mm	5	39	12.8
(+) cAF, (+) LVDd≥65mm	8	28	28.6

Figure 4. Subgroup analysis in groups A and B. (**A**) Prevalence of fatal arrhythmic events (FAE) in the following 4 groups with group C as reference: (1) cAF not present and LVDd <65 mm; (2) cAF alone; (3) LVDd ≥65 mm alone; (4) cAF and LVDd ≥65 mm. (**B**) Kaplan-Meier curves for FAE in the 4 groups with group C as the reference. Blue, no cAF and LVDd <65 mm; yellow, cAF alone; green, LVDd ≥65 mm; red, cAF and LVDd ≥65 mm; black, group C. (**C**) Relative hazard ratio (HR) for FAE as compared with no cAF and LVDd <65 mm. cAF, chronic atrial fibrillation; CI, confidence interval; LVDd, end-diastolic left ventricular diameter.

>0.12 s, and AF).[42] Watanabe et al proposed 5 risk factors for SCD in CHF patients, including LVEF <30%, LVDd >60 mm, BNP >200 pg/ml, NSVT, and diabetes mellitus. They showed that the annual mortality from sudden death was 11% in patients with ≥3 risk factors and 1.4% in patients with ≤2.[41] In the present study, the presence of cAF or LVDd ≥65 mm had higher relative HR and their combination achieved the highest HR.

To the best of our knowledge, this is the first study on the risk stratification of CHF patients eligible for prophylactic ICD implantation in clinical practice in Japan.

Study Limitations

Several limitations should be mentioned for the present study. First, the number of group A and B patients was smaller than that of group C, and thus the statistical power might not be sufficient to detect a difference between groups A and B. Second, we included the patients with CRT-D, although CRT itself could reduce the prevalence of FAE due to improvement of LVEF and/or circulatory dynamics. Carson et al, however, reported that CRT-D, but not CRT alone, significantly reduced SCD in CHF patients.[43] Thus, we consider that the impact of CRT was, if any, small in the present study. Third, we might have underestimated the prevalence of NSVT in the present study. NSVT, which is a factor needed for class I indication in the JCS guidelines, was not an independent predictor in the present study. This could be partially due to the insufficient data collection of NSVT at enrollment, given that 24-h Holter ECG at enrollment was performed in only 60% of the patients in the present study. Fourth, we were unable to evaluate the predictive power of EPS, which is also one of the class I indications of prophylactic ICD implantation in the JCS guidelines, due to the small number of patients with prophylactic ICD who underwent EPS. Fifth, we examined only the combined patient group of IHD and NIDCM. Thus, further study is needed to evaluate the prevalence and risk stratification of FAE in each structural heart disease.

Conclusions

The present study validates the current JCS guidelines for prophylactic ICD implantation in CHF patients and also demonstrates the underuse of ICD in real-world clinical practice in Japan. Furthermore, the combination of cAF and LVDd ≥65 mm may be a useful predictor to stratify the risk of FAE in Japanese CHF patients eligible for ICD implantation.

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Supplementary Files

Supplementary File 1

Appendix S1. Organization of the CHART-2 Study

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-14-0925