Journal of Arrhythmia 29 (2013) 168–174

Contents lists available at SciVerse ScienceDirect

Journal of Arrhythmia

journal homepage: www.elsevier.com/locate/joa

Original Article

Current status of cardiac resynchronization therapy with defibrillators and factors influencing its prognosis in Japan ☆

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ARTICLE INFO

Article history:
Received 9 April 2013
Accepted 17 April 2013
Available online 17 May 2013

Keywords:
Cardiac resynchronization therapy with defibrillator
Registration
Appropriate shock
Mortality

ABSTRACT

Purpose: The purpose of this study was to clarify the prognosis of cardiac resynchronization therapy with defibrillators (CRT-Ds) in Japan.
Methods: We selected 384 patients implanted with a CRT-D device from the observation database ($n=1482$) of the Japanese Cardiac Device Therapy Registry. We investigated the CRT criteria, including the presence of New York Heart Association (NYHA) class III/IV symptoms, left ventricular ejection fraction (LVEF) ≤35%, and QRS duration ≥120 ms. The patients were divided into 2 groups: the group fulfilling all of the 3 criteria (Group A, $n=229$) and the group not fulfilling the criteria (Group B, $n=155$). We compared mortality and appropriate shock rates between the 2 groups.
Results: There was no significant difference in mortality (17.9% vs. 13.5%) or appropriate shock rates (32.5% vs. 31.6%) during the observation period of 29.0 ± 15.7 months between the 2 groups. A logistic multivariate analysis showed that appropriate shocks (hazard ratio [HR]=1.85) and class III antiarrhythmic agents (HR=2.33) were independently associated with all-cause death, and that age ≥70 years (HR=0.55), male gender (HR=2.07), and presence of a single-chamber device (HR=1.78) were associated with appropriate shocks. The prognosis of Group A was better than that of the COMPANION trial.
Conclusions: Japanese patients with CRT-D devices had a better prognosis than did those in the COMPANION trial, but no significant differences were observed between patients fulfilling and those not fulfilling the above mentioned criteria.

1. Introduction

Cardiac resynchronization therapy (CRT) with an implantable cardioverter-defibrillator (ICD) or without an ICD (CRT-P) is recommended to reduce morbidity and mortality in patients who have New York Heart Association (NYHA) class III/IV heart failure, are symptomatic despite optimal medical therapy, and have a reduced left ventricular (LV) ejection fraction (LVEF) and electrical dyssynchrony [1–3]. The effects of CRT are reflected mainly by the degree and location of the dyssynchrony and by the successful insertion of lead into the optimal LV lead site [4,5]. No significant differences have been observed between the right ventricular apical and non-apical positions of the lead tip in a previous study [6].

In Japan, ICDs were approved by the Japanese Ministry of Health, Labor and Welfare (MHLW) in 1996. CRT-P and CRT with an ICD (CRT-D) were also approved in 2004 and 2006, respectively.

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http://dx.doi.org/10.1016/j.joa.2013.04.006

The Japan Cardiac Device Treatment Registry (JCDTR) was established by the Japan Heart Rhythm Society for investigating the actual conditions of implantable devices (ICD/CRT-D) [7]. New guidelines were set forth by the Japanese Circulation Society in 2007 [8] and were then updated in 2011 [9].

The number of CRT-D implantations has markedly increased since 2006 when they were approved by the MHLW. In particular, primary prevention using CRT-D devices has dramatically increased over the last 5 years in Japan according to the JCDTR enrollment database [10], but this database has shown no significant changes in the criteria involving the QRS duration, LVEF, and NYHA class in patients with a CRT-D device over these 5 years [11]. Thus, the increase in the number of CRT-D device implantations for primary prevention did not result from an increase in the number of patients with a relatively early phase of heart failure and electrophysiologic disturbance in Japan [11].

The prognosis and occurrence of appropriate shocks in the therapy for ventricular tachycardia/ventricular fibrillation are not clear in patients with implanted devices in Japan. Therefore, the purpose of this study was to clarify the prognosis in patients who were implanted with a CRT-D device in Japan.

2. Methods

2.1. Patient population

Between January 1, 2006 and December 31, 2010, 384 patients implanted with CRT-D devices were selected from 1482 patients from the JCDTR observation database (ICDs and CRT-Ds) from 16 facilities of the Devise Assessment Committee of the Japanese Heart Rhythm Society (JHRS) (Appendix). Data were collected by means of a retrospective multicenter study. Informed consent was waived for the analysis of preexisting clinical data.

The distribution of underlying heart disease in CRT-D patients was investigated in the primary prevention and secondary prevention groups. Underlying heart disease was classified into ischemic heart disease (IHD), dilated cardiomyopathy (DCM), secondary cardiomyopathy (2ndCM), hypertensive heart disease (HHD), valvular heart disease (VHD), congenital heart disease (CHD), hypertrophic cardiomyopathy (HCM), and miscellaneous (micell).

The prognoses of the survival rate and appropriate shocks were studied as the primary endpoints, and clinical variants associated with mortality and appropriate shock rate were then investigated. In this study, patients were divided into 2 groups according to the CRT-D criteria (NYHA class III/IV symptoms, LVEF≤35%, and QRS width ≥120 ms, as per the Japanese Circulation Society (JCS) 2011 Guidelines [9]): Group A comprised 229 patients who fulfilled all of the 3 criteria, and Group B comprised 155 patients who fulfilled 2 or fewer of the 3 criteria. Clinical characteristics, survival, and appropriate shock rate were compared between the 2 groups.

In this study, a single-chamber ICD was defined as an ICD with no lead placed in the atrium. An appropriate shock was defined as shock therapy or antitachycardia pacing for ventricular tachycardia and/or ventricular fibrillation.

2.2. Statistical analysis

The data are presented as the mean ± standard deviation (SD). The chi-square test and Student *t*-test for independent variables were used for comparisons between the groups. Kaplan–Meier curves with survival rates and appropriate shocks as the outcomes of interest were calculated. Further, the log-rank test statistic was used to determine the statistical significance of unadjusted differences in the time to the event. A univariate analysis (Mantel–Haenszel method) of the clinical variables in the JCDTR questionnaire followed by multivariate analyses (linear model method) of the clinical variables showing a significant difference in the univariate analysis were performed using the SPSS software (SPSS 16.0 Family for Windows, MapInfo, NY) for evaluating the association with mortality and appropriate shocks in the CRT-D patients. A value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Distribution of the underlying heart disease in the CRT-D patients

A higher number of patients was present in the primary prevention group ($n=247$; 64%) than in the secondary prevention group ($n=137$; 46%), as shown in Fig. 1. The percentage of IHD events was lower in the primary prevention group (19%) than in the secondary prevention group (31%). On the other hand, the percentage of CM events (DCM+2ndCM) was higher in the primary prevention group (66%) than in the secondary prevention group (54%). The percentage of IHD plus CM events in the primary prevention group (85%) was similar to that in the secondary prevention group (85%).

3.2. Clinical characteristics and medications

There were no significant differences in age, percentage of patients in the primary prevention group, and percentage of IHD events and single-chamber CRT-D devices between Groups A and

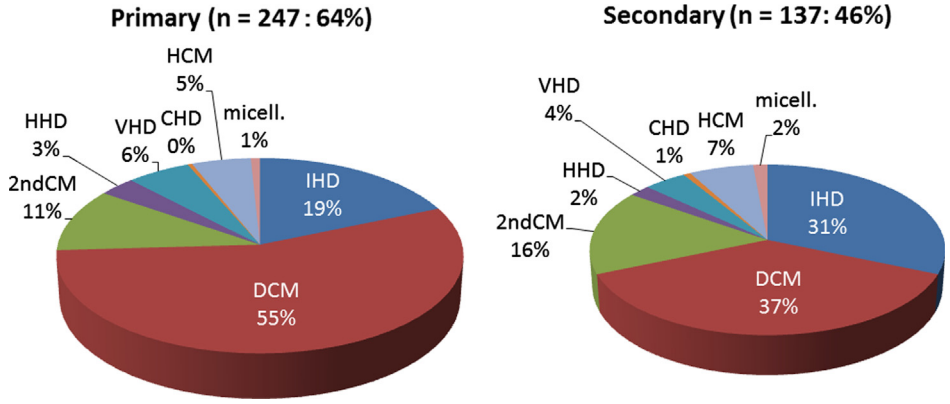

Fig. 1. Distribution of the underlying heart disease in the primary prevention and secondary prevention groups. Primary: primary prevention group; secondary: secondary prevention group; IHD: ischemic heart disease; DCM: dilated cardiomyopathy; 2ndCM: secondary cardiomyopathy; HHD: hypertensive heart disease; VHD: valvular heart disease; CHD: congenital heart disease; HCM: hypertrophic cardiomyopathy; micelle: miscellaneous.

B (Table 1). However, as expected, there were significantly more patients with NYHA class III/IV heart failure, lower LVEF, and wider QRS duration in Group A than in Group B ($p=0.0001$).

There was no significant difference in the use of medications, except for diuretics, ACE inhibitors, and class III antiarrhythmic drugs, between the 2 groups (Table 2).

3.3. Survival rate and appropriate shock rate

Thirty-eight patients in the primary prevention group and 24 patients in the secondary prevention group died during the observation period of 29.0 ± 15.7 months. There was no significant difference in the survival rate between the primary and secondary prevention groups (Fig. 2, left panel). The appropriate shock rate in the primary prevention group was 29.7% ($n=73$), which was lower than that in the secondary prevention group (36.5%, $n=50$). However, the difference did not reach statistical significance in the Kaplan–Meier curves ($p=0.213$, Fig. 2, right panel).

Forty-one Group A patients (17.9%) and 21 Group B patients (13.5%) died during the observation period (Fig. 3, left panel). The survival rate after 40 months was worse in Group A than in Group B, but no significant difference was observed ($p=0.182$) in the Kaplan–Meier curves. Further, 74 Group A patients (32.5%) and 49 Group B patients (31.6%) received appropriate shocks during the observation period (Fig. 3, right panel). The appropriate shock rate after 40 months was higher in Group A than in Group B, but no significant difference was observed in the Kaplan–Meier curve analysis between the 2 groups ($p=0.853$).

Table 1
Clinical characteristics.

	Group A ($n=229$)	Group B ($n=155$)	All ($n=384$)	p, Groups A vs. B
Age	63 ± 12	61 ± 13	62 ± 13	0.117
Male (%)	158 (69)	114 (74)	272 (78)	0.198
Primary (%)	145 (63)	102 (66)	247 (64)	0.349
Underlying heart disease				
IHD (%)	55 (24)	34 (22)	89 (23)	0.658
non-IHD (%)	174 (76)	121 (78)	295 (77)	
NYHA class				
I/II	0/0	19/94	19/94 (29%)	0.0001
III/IV	199/30	38/4	237/34 (71%)	
LVEF (%)	23 ± 7	32 ± 12	27 ± 10	0.0001
QRS duration (ms)	158 ± 27	142 ± 39	152 ± 33	0.0001
Single chamber (%)	52 (23)	0 (0)	92 (24)	0.281

Primary: primary prevention of cardiac resynchronization therapy with defibrillators (CRT-D); IHD: ischemic heart disease; non-IHD: non-ischemic heart disease; NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; single chamber: single-chamber CRT-D.

Table 2
Medications.

	Group A ($n=229$)	Group B ($n=155$)	All ($n=384$)	p, Groups A vs. B
Diuretics (%)	192 (84)	102 (66)	294 (77)	0.0001
Spironolactone (%)	99 (43)	60 (39)	159 (41)	0.219
ACE (%)	102 (45)	53 (34)	155 (40)	0.027
ARB (%)	88 (38)	65 (42)	153 (40)	0.280
ACE and/or ARB (%)	183 (80)	115 (74)	298 (78)	0.117
Beta-blockers (%)	180 (79)	111 (72)	291 (76)	0.074
Digitalis (%)	55 (24)	37 (24)	92 (24)	0.710
Nitrites (%)	19 (8)	10 (6)	29 (8)	0.321
Alpha-blockers (%)	0 (0)	0 (0)	0 (0)	–
Antiarrhythmic agents				
Class I				
A (%)	1 (0.4)	3 (2)	4 (1)	0.307
B (%)	8 (3)	3 (2)	11 (3)	0.285
C (%)	1 (0.4)	0 (0)	1 (0.2)	0.596
Class II (%)	180 (78)	111 (72)	291(76)	0.074
Class III (%)	113 (49)	62 (40)	175 (46)	0.044
Class IV (%)	13 (6)	14 (9)	27 (7)	0.145
Statins (%)	55 (24)	37 (24)	92 (24)	0.537
Warfarin (%)	139 (61)	81 (53)	220 (57)	0.062
Antiplatelet agents (%)	58 (25)	36 (23)	94 (24)	0.365

ACE: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; LVEF: left ventricular ejection fraction.

3.4. Clinical variants associated with mortality and appropriate shocks in the CRT-D patients

None of the male patients, primary prevention group patients, and patients with LVEF≤35%, NYHA class III/IV heart failure, and QRS duration ≥120 ms showed any significant association with all-cause death; however, age ≥70 years, incidence of appropriate shocks, S-creatinine level ≥1.5 mg/dl, use of class III antiarrhythmic drugs, and presence of a single-chamber CRT-D showed significant association with all-cause death in the univariate analysis (Table 3). Only incidence of appropriate shocks (hazard ratio [HR]=1.85, 95% confidence interval [CI]: 1.04–3.28, $p=0.036$) and use of class III drugs (HR=0.004, 95% CI: 1.32–4.13) were independently associated with all-cause death (Table 3). Single-chamber CRT-D devices had a tendency to be associated with all-cause death (HR=1.73; 95% CI: 0.94–3.19).

Primary prevention and presence of LVEF≤35%, NYHA class III/IV heart failure symptoms, and QRS duration ≥120 ms did not show significant association with the incidence of appropriate shocks; however, age ≥70 years, male gender, and presence of a single-chamber CRT-D device showed a significant difference in the univariate analysis (Table 4). Only age ≥70 years (HR=0.55, 95% CI: 0.33–0.91), male gender (HR=2.07, 95% CI: 1.23–3.48), and presence of a single-chamber CRT-D device (HR=1.78, 95% CI: 1.08–2.93) were independently associated with appropriate shocks in the CRT-D patients (Table 4).

3.5. Comparison of the prognosis between the COMPANION trial [2] and Group A from the JCDTR observation database

We compared the clinical characteristics between the Group A patients from the JCDTR and patients from the COMPANION trial (Table 5). There was no significant difference in the percentage of male subjects between the 2 studies. Although the percentage of IHD events was significantly higher ($p=0.0001$) in the COMPANION trial [2] than in Group A from the JCDTR, the ratios of the NYHA classification, LVEF, and QRS duration were similar between the 2 groups. For pharmacological therapy, angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers, loop diuretics, and spironolactone were used more often in the COMPANION trial than in Group A from the JCDTR. Beta-blockers were used more in Group A from the JCDTR than in the COMPANION trial (Table 5). All-cause death in Group A from the JCDTR was similar to that in the COMPANION trial; however, the observation period for the JCDTR was almost double that of the COMPANION trial. Therefore, the annual mortality rate was better in Group A from the JCDTR (3.5%/year) than in the COMPANION trial (7.4%/year).

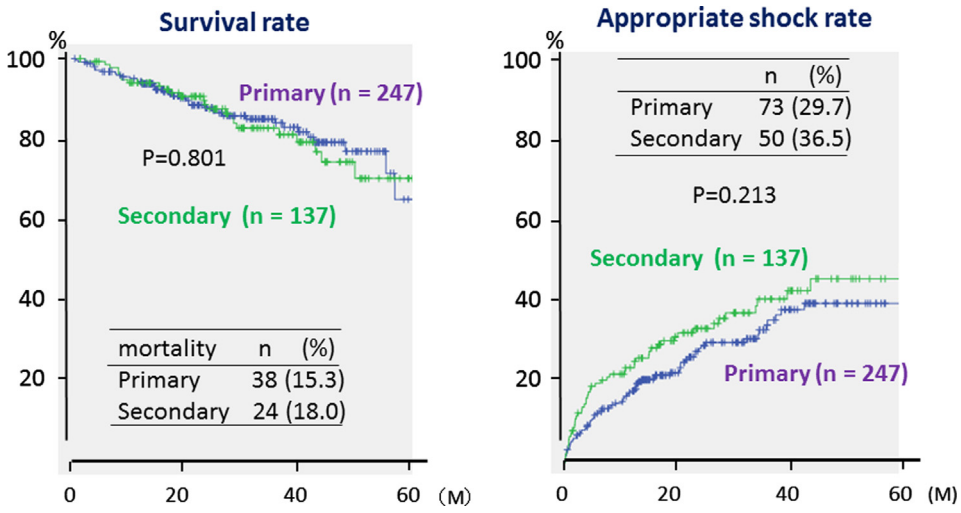

Fig. 2. Survival rate and appropriate shock rate in the primary prevention and secondary prevention groups. Survival rate: rate of all-cause death; appropriate shock: shock therapy for the treatment of ventricular tachycardia and ventricular fibrillation.

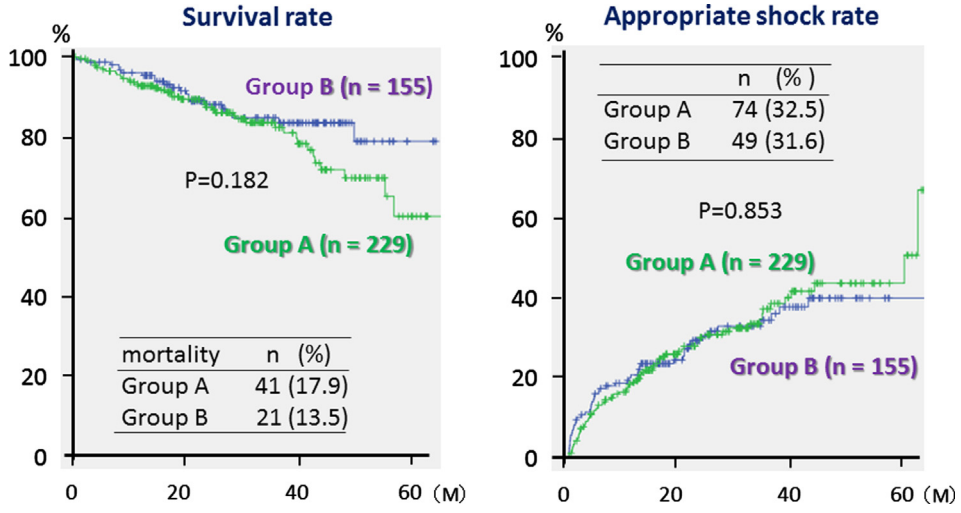

Fig. 3. Survival rate and appropriate shock rate in Groups A and B. See Fig. 2 for the abbreviations.

Table 3
Clinical variants associated with mortality in patients with CRT-D.

	Univariate analysis					Multivariate analysis				
	HR	95% CI			*p*	HR	95% CI			*p*
Age ≥70 years	0.50	0.26	–	0.99	0.042	0.57	0.29	–	1.13	0.108
Male	1.35	0.72	–	2.53	0.347					
Primary	1.17	0.67	–	2.05	0.586					
LVEF≤35%	1.34	0.58	–	3.13	0.493					
NYHA III/IV	1.24	0.67	–	2.30	0.495					
QRS duration ≥120 ms	0.62	0.30	–	1.29	0.199					
IHD	0.84	0.45	–	1.58	0.592					
Appropriate shock	2.10	1.21	–	3.65	0.008	1.85	1.04	–	3.28	0.036
S-creatinine ≥1.5 mg/dl	2.82	1.24	–	6.38	0.011	2.03	0.82	–	5.00	0.125
Class III drugs	2.32	1.32	–	4.06	0.003	2.33	1.32	–	4.13	0.004
Single chamber	1.81	1.00	–	3.26	0.046	1.73	0.94	–	3.19	0.080

HR: hazard ratio; CI: confidence interval; Primary: primary prevention with CRT-D; LVEF: left ventricular ejection fraction; IHD: ischemic heart disease; S-creatinine: serum creatinine; single chamber: single-chamber CRT-D.

4. Discussion

4.1. General considerations for CRT-D

CRT is known to improve LV systolic function, heart failure, symptoms, quality of life, and prognosis in patients with moderate or severe heart failure, depressed systolic function, and a wide QRS complex [1–3]. It is necessary to implant a CRT-D or ICD device in patients with severe LV dysfunction, because CRT improves the prognosis of patients. A meta-analysis of all-cause death and admission rate showed no significant difference between the use of an ICD and use of a CRT-D device in patients with LV dysfunction

Table 4
Clinical variants associated with appropriate shocks in patients with CRT-D.

	Univariate analysis					Multivariate analysis				
	HR	95% CI			*p*	HR	95% CI			*p*
Age≥70 years	0.54	0.33	–	0.88	0.013	0.55	0.33	–	0.91	0.020
Male	1.86	1.13	–	3.08	0.015	2.07	1.23	–	3.48	0.006
Primary	1.34	0.86	–	2.09	0.189					
LVEF≤35%	1.60	0.82	–	3.11	0.164					
NYHA III/IV	0.97	0.61	–	1.55	0.903					
QRS duration≥120 ms	0.59	0.32	–	1.09	0.090					
S-creatinine≥1.5 mg/dl	1.87	0.92	–	3.83	0.083					
Class III drugs	1.23	0.73	–	1.73	0.585					
Single chamber	1.79	1.10	–	2.91	0.018	1.78	1.08	–	2.93	0.024

HR: hazard ratio; CI: confidence interval; Primary: primary prevention with CRT-D; LVEF: left ventricular ejection fraction; S-creatinine: serum creatinine; single chamber: single-chamber CRT-D.

Table 5
Comparison of the clinical characteristics between the COMPANION and JCDTR (Group A) trials.

n	COMPANION CRT-D Therapy 595	JCDTR (Group A) CRT-D Therapy 229	*p*
Age (years)	66	63	–
Male (%)	67	69	0.594
Ischemic heart disease (%)	55	24	0.0001
NYHA class III	86%	87%	0.751
LVEF (%)	22	23	–
QRS duration (ms)	160	158	–
Pharmacological therapy (%)			
ACE	69	45	0.0001
ACE and/or ARB	90	80	0.0001
Beta-blockers	68	79	0.002
Loop diuretics	97	84	0.0001
Spironolactone	55	43	0.002
All-cause death, *n* (%)	105 (17.6)	41 (17.9)	–
Follow-up (months)	15.7	29.0	–

–: Cannot be calculated; ACE: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; LVEF: left ventricular ejection fraction.

[12]. Therefore, the difference in the prognosis between the patient groups implanted with ICD and CRT-D devices is unclear.

Some investigators concluded that CRT was not associated with a decrease in the frequency of ventricular arrhythmias or appropriate device therapies [13], and that CRT did not reduce the incidence of atrial fibrillation [14]. On the other hand, arrhythmia frequency and the number of appropriate ICD treatments decreased after an upgrade to a CRT-ICD device as a heart failure treatment. Thus, apart from the hemodynamic benefits, CRT may also ameliorate ventricular tachyarrhythmia susceptibility in heart failure patients [15]. In a recent study, after an upgrade from an ICD to a CRT-D device, responders to CRT showed a trend toward a decrease in the frequency of ventricular arrhythmias, and non-responders to CRT showed a significant increase in ventricular arrhythmias requiring appropriate device therapy [16]. Further, CRT-D decreased the risk of heart failure events in relatively asymptomatic patients with a low ejection fraction and wide QRS complex [17–19].

CRT did not improve clinical outcomes or LV remodeling in patients with an LVEF≤35% or symptoms of heart failure, but CRT in patients with a QRS duration of <120 ms might be associated with potential harm [20]. The ACC/AHA and ESC guidelines in 2008 postulated that CRT was recommended in patients with QRS duration of ≥120 ms [21,22]. However, only a QRS duration ≥150 ms and a left bundle branch block (LBBB) pattern showed a significant difference in the prognosis between ICD and CRT-D patients [17,18]. Presence of NYHA class II symptoms showed a significant difference in the prognosis between ICD and CRT-D patients [17–19]. The results of mega-trials related to CRT or CRT-D had a strong influence on the guidelines for CRT-D/CRT-P. According to the 2011 Update from the Heart Failure Society of America [23], CRT is recommended in patients who have a widened QRS interval of ≥150 ms (changed from ≥120 ms, specified in the 2010 guidelines) that is not due to right bundle branch block (newly added criterion) and who have persistent NYHA class II symptoms (newly added criterion for biventricular pacing therapy recommended in the 2010 guidelines). According to the 2012 ACCF/AHA/HRS guidelines [24], CRT is indicated as class I for patients who have an LVEF≤35%, sinus rhythm, LBBB with a QRS duration ≥150 ms, and NYHA class II, III, or ambulatory IV heart failure symptoms: symptoms on guideline-directed medical therapy (Level A for NYHA class III/IV; Level B for NYHA class II).

On the other hand, the 2011 update of the JCS guidelines [9] stated that CRT is recommended in patients with LVEF≤35%, QRS duration ≥120 ms, NYHA class III or ambulatory IV heart failure symptoms despite optimal medical therapy, and sinus rhythm. In the present study, the patients were divided into 2 groups on the basis of whether they fulfilled the following 3 criteria: LVEF≤35%, QRS duration ≥120 ms, and NYHA class III/IV heart failure symptoms, as specified by the JCS guidelines [9].

4.2. Actual conditions of the implantation of CRT-D devices in Japan

The number of CRT-D device implantations has increased dramatically in not only Western and European countries but also Japan [10]. Several reasons have been considered. First, much evidence has proven that CRT-D/CRT-P improves prognosis in patients with heart failure and severe LV dysfunction. Second, CRT-D might be superior to CRT-P in improving prognosis and decreasing sudden cardiac death. Several recent trials [17–19] have also shown the potentially better effects of CRT-D, compared to those of CRT-P, even in patients with early-stage heart failure. However, the 3 criteria (QRS duration, LVEF, and NYHA classification) for CRT-P implantations have not changed over the last 5 years according to the JCDTR enrollment database in Japan. Although primary prevention with CRT-D has increased over the last 5 years in Japan, this has not resulted from an increase in patients with a relatively early phase of heart failure and electrophysiologic disturbance [11].

In a previous study of the distribution of underlying heart diseases by routine clinical practice, the percentage of IHD events was observed to be 62% in the Netherlands [25]. The percentage of IHD events was 30% in the primary prevention group and 33% in the secondary prevention group. On the other hand, in the present study, the percentage of IHD events was 19% in the primary prevention group and 31% in the secondary prevention group. Thus, the percentage of IHD events in CRT-D patients is relatively

lower in Japan than in Western countries, which is similar to the result obtained with ICD use [10].

4.3. Survival rate and appropriate shock rate

In this study, no significant difference was observed in the survival rate for at least up to 40 months between patients who qualified for CRT-D device implantation and those who did not. On the other hand, no significant difference was observed in the survival rate between the primary prevention and secondary prevention groups. However, in the real-world setting, this fact does not seem surprising [25].

In a comparison with the COMPANION trial (13.5%/year), the annual mortality rate in Group A of the JCDTR (7.4%/year) was revealed to have a better prognosis. Some baseline variables that differed in our patients would be expected to lead to worse outcomes (an older age and higher percentage of ischemic cardiomyopathy). These differences in the baseline characteristics may partially explain the better survival rate in our patients as compared with that in the COMPANION trial patients.

A single-center trial [23] in the USA also reported that survival and cardiovascular hospitalization outcomes in the real-world clinical setting are as good as, or better than, those demonstrated in the COMPANION research trial [2]. They divided their patients into 3 groups: group 1 ($n=429$), standard indications; group 2 ($n=144$), a subgroup of the group-1 patients who met the COMPANION entrance criteria; and group 3 ($n=595$), a cohort both with and without a propensity-matching statistical analysis. Survival was better in group 1 (annual mortality rate 8.5%) than in group 3, but the mortality rates in the real-world setting were similar to those in the COMPANION trial, once adjustments were made for the differences in the baseline characteristics [23].

In a real-world registry [26] comprising 14,946 patients, the annual mortality rate for any number of baseline characteristics, including LVEF (24.7%), QRS duration (157 ms), beta-blocker use (78.9%), and angiotensin-converting enzyme inhibitor and/or angiotensin II receptor blocker use (74.2%), excluding age (73.0 years of age), was similar to that of our patients, whereas the mortality rate at 3 years was 31.8% (10.6% per year). The authors of that study concluded that the real-world mortality rates at 3–4 years after the CRT-D implantation appear to be higher than previously recognized [26].

Between 1996 and 2010, from a total of 2859 patients with an implanted ICD or CRT-D device at the Leiden University Medical Center, The Netherlands, during a median follow-up of 3.4 years (interquartile range, 1.7–5.7 years) [25], 107 (14%) primary prevention ICD recipients, 253 (28%) secondary prevention ICD recipients, and 302 (25%) CRT-D recipients died (all-cause death) [25]. The annual mortality rate was 2.9% in the primary prevention ICD patients, 4.5% in the secondary prevention ICD patients, and 6.9% in the CRT-D patients. The annual mortality rate of these CRT-D patients was slightly better than that of our patients.

In the present study, the annual rate of appropriate shocks in the primary prevention group (12.3%/year) was better than that in the secondary prevention group (15.1%/year), but this difference was not statistically significant in the Kaplan–Meier curves. There was no significant difference in the appropriate shock rate between Group A (13.4%/year) and Group B (12.9%/year).

For instance, in 2134 ICD recipients (80% men; mean age, 63 ± 12 years) at the Leiden University Medical Center between 1996 and 2008 [27], the 5-year cumulative incidence of appropriate shocks was 20% (95% CI: 16–23%) in primary prevention patients and was 37% (95% CI: 33–41%) in secondary prevention patients. Secondary prevention patients exhibited more than double the risk of appropriate shocks during the long-term follow-up (HR: 2.3, 95% CI: 1.9–2.9; $p<0.001$) [27]. The average annual rate of appropriate shocks in patients who received primary ICD therapy was 5.1% during 5 years of follow-up in the Sudden Cardiac Death in Heart Failure (SCD-HeFT) Trial [28].

The annual rate of appropriate shocks was higher in our study than in the Leiden University Medical Center data [27] and SCD-HeFT Trial [28], because the clinical setting was worse in the CRT-D patients than in the ICD patients. The CRT-D patients had more severe heart failure and a wider QRS duration than did the ICD patients.

4.4. Clinical variables associated with mortality and event rates

Many clinical variables such as the degree of heart failure, QRS duration, QRS morphology, sex, lead placement, atrial fibrillation, and other patient selection criteria were associated with mortality in the CRT-D patients. A recent study [23] postulated that a QRS duration of ≥150 ms, LBBB, female gender, LV lead positioned at sites other than the apical region, NYHA classes II–III and ambulatory IV heart failure symptoms, and sinus rhythm were strongly associated with a better prognosis in CRT-D patients. In this study, incidence of appropriate shocks and use of class III antiarrhythmic drugs were independently associated with mortality in CRT-D patients. Appropriate shocks have been known to worsen prognosis in a previous study [29]. The reason underlying the poor prognosis in patients using class III antiarrhythmic agents is complex. The patients requiring class III antiarrhythmic treatment had a substrate for lethal tachyarrhythmias related to appropriate shocks, and that might have led to poor prognosis in the CRT-D patients.

In the multivariate analysis in the present study, male gender and a single-chamber ICD were independently associated with appropriate shocks in CRT-D patients. Further, age ≥70 years had an odds ratio of 0.55 (95% CI: 0.33–0.91). This led to a propensity for cardiac events in the younger patients (<70 years old), because younger patients had a more active lifestyle than did the older patients. Although both men and women benefit from CRT, some data suggest that women may benefit to a greater degree than may men [17,30]. Additionally, women have experienced greater improvements in echocardiographic measurements of reverse remodeling [30]. A single-chamber ICD in this study was defined as an ICD with no lead placed in the atrium. We did not determine whether single-chamber ICD implantation was due to patients having paroxysmal, persistent, or permanent atrial fibrillation or difficulty in the placement of the atrial leads. Thus, this result indicates that dual-chamber ICDs have a better prognosis for appropriate shocks than do single-chamber ICDs.

4.5. Limitations

This study was a multicenter, retrospective study that evaluated all patients who underwent CRT-D device implantations at 16 hospitals. Many hospitals were university hospitals that might have been actively involved in CRT-D research for many years and might have developed a number of protocols devised to manage patients treated with CRT-D devices. Thus, our findings may not reflect the experience of the typical community-based CRT-D programs in Japan. A larger multicenter, prospective study will be necessary to determine more accurate information regarding the actual conditions and prognosis of CRT-D treatment in Japan.

5. Conclusions

Mortality was associated with appropriate shocks and use of class III drugs, and appropriate shocks were associated with a younger age, male gender, and single-chamber CRT-D devices.

Japanese patients with implanted CRT-D devices showed no significant differences in the prognosis irrespective of whether the criteria were fulfilled. Japanese patients with implanted CRT-D devices had a better prognosis than did those in the COMPANION trial [2].

Conflict of interest

The authors have no financial conflicts of interest to disclose.

Appendix

The hospitals participated in this study are given in alphabetical order.

Hiroshima University, Hokkaido University, Itabashi Central Hospital, Jichi Medical University, Kitasato University, Kyorin University, Nagoya University, National Cardiovascular Center, Niigata University, Tokyo Women's Medical University, Tsukuba University, University of Occupational and Environmental Health, Okayama University, Osaka Medical University, Osaka City University, and Yamaguchi University.

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