Survival and Heart Failure Hospitalization in Patients With Cardiac Resynchronization Therapy With or Without a Defibrillator for Primary Prevention in Japan

— Analysis of the Japan Cardiac Device Treatment Registry Database —

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Background: Randomized control trials comparing the effectiveness of cardiac resynchronization therapy devices, with (CRT-D) or without (CRT-P) a defibrillator, are scarce in heart failure patients with no prior sustained ventricular tachyarrhythmias.

Methods and Results: The Japan Cardiac Device Treatment Registry (JCDTR) has data for 2714 CRT-D and 555 CRT-P recipients for primary prevention with an implantation date between January 2011 and August 2015. Of these patients, follow-up data were available for 717. Over the mean follow-up period of 21 months, Kaplan-Meier curves of survival free of combined events for all-cause death or heart failure hospitalization (whichever came first) diverged between the CRT-D (n=620) and CRT-P (n=97) groups with a rate of 22% vs. 42%, respectively, at 24 months (P=0.0011). However, this apparent benefit of CRT-D over CRT-P was no longer significant after adjustment for covariates. With regard to mortality, including heart failure death or sudden cardiac death, there was no significant difference between the 2 groups.

Conclusions: In patients without sustained ventricular tachyarrhythmias enrolled in the JCDTR, there was no significant difference in mortality between the CRT-D and CRT-P groups, despite a lower trend in CRT-D recipients. This study was limited by large clinical and demographic differences between the 2 groups.

Key Words: Cardiac resynchronization therapy (CRT); CRT defibrillator (CRT-D); CRT pacemaker (CRT-P); Primary prevention

Cardiac resynchronization therapy (CRT) using an atrial-synchronized biventricular pacemaker (CRT-P) has been the established treatment for patients with symptomatic heart failure, left ventricular ejection fraction (LVEF) $\leq 35\%$, and a QRS duration ≥ 130 ms since the Multicenter InSync Randomized Clinical

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Evaluation (MIRACLE) study was reported in 2002.¹ The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) study proved a better

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	CRT-D (n=620)	CRT-P (n=97)	P value
Age (years)	66.8±11.2	77.0±10.2	<0.0001
Male	476 (76.8)	59 (60.8)	0.0008
Underlying heart disease			0.197
Ischemic	173 (27.9)	21 (21.6)	
Non-ischemic	447 (72.1)	76 (78.4)	
LVEF (%)	26.5±9.0	33.0±11.1	<0.0001
LVEF ≤35%	553 (89.2)	68 (70.1)	<0.0001
NYHA class			0.803
I	8 (1.3)	2 (2.1)	
II	165 (26.6)	22 (22.7)	
III	383 (61.8)	63 (64.9)	
IV	64 (10.3)	10 (10.3)	
Heart rate (beats/min)	71.1±17.2	74.0±19.1	0.134
QRS duration (ms)	153.5±30.7	157.9±24.7	0.172
QRS duration (ms) class			0.023
<120	76 (12.3)	3 (3.1)	
120–149	203 (32.7)	32 (33.0)	
≥150	341 (55.0)	62 (63.9)	
QT interval (ms)	455.3±55.4	463.2±48.3	0.185
Atrial lead			0.672
Absent	92 (14.8)	16 (16.5)	
Present	528 (85.2)	81 (83.5)	
NSVT ^A	179 (66.5) ^A	4 (26.7) ^A	0.0017
AF	82 (13.2)	12 (12.4)	0.817
Type of AF			0.705
Paroxysmal/persistent	32 (39)/50 (61)	4 (33)/8 (67)	
Diabetes mellitus	195 (31.5)	28 (28.9)	0.609
Hypertension	242 (39.0)	53 (54.6)	0.0037
Dyslipidemia	186 (30.0)	28 (28.9)	0.820
Hyperuricemia	127 (20.5)	17 (17.5)	0.499
Cerebral infarction	44 (7.1)	6 (6.2)	0.743
Peripheral artery disease	19 (3.1)	4 (4.1)	0.582
BNP (pg/mL) ^B	781.0±1,324.8	820.1±822.1	0.799
Hemoglobin (g/dL)	12.7±2.1	12.2±1.9	0.0243
Creatinine (mg/dL)	1.48±1.48	1.45±1.60	0.858
Goldenberg score ^C	2.3±1.1	2.7±0.9	0.0008

Data are presented as the mean±SD or as n (%). ^AInformation regarding the presence or absence of non-sustained ventricular tachycardia (NSVT) was available in 269 patients implanted with a cardiac resynchronization therapy defibrillator (CRT-D) and 15 patients implanted with a cardiac resynchronization therapy pacemaker (CRT-P). ^BB-Type natriuretic peptide (BNP) data were missing for 67 CRT-D recipients and 18 CRT-P recipients. ^CThe original risk score model comprised 5 clinical factors, namely New York Heart Association (NYHA) Class ≥II, atrial fibrillation (AF), QRS duration >120 ms, age >70 years, and blood urea nitrogen (BUN) >26 mg/dL. Because BUN data were not collected in the Japan Cardiac Device Treatment Registry (JCDTR) database, blood creatinine >1.5 mg/dL was used as a risk factor instead of BUN. Data on all 5 factors were available for 609 CRT-D recipients and 95 CRT-P recipients. LVEF, left ventricular ejection fraction.

prognosis of moderate-to-severe heart failure (New York Heart Association (NYHA) Class III or IV) patients using CRT compared with optimal pharmacologic therapy alone, especially when an implantable cardioverter-defibrillator (ICD) backup was present (CRT-D).² In addition, CRT-P was shown to reduce the risk of death in advanced heart failure patients and in patients with cardiac dyssynchrony due to a prolonged QRS interval of at least 120 ms in the Cardiac Resynchronization-Heart Failure (CARE-HF) study.³ However, randomized controlled trials directly comparing the efficacy of CRT-D with that of CRT-P are extremely scarce.^{2,4,5}

In the COMPANION study, CRT-P decreased the risk of the primary composite endpoint of death from or hospitalization for any cause, as did CRT-D.² With regard to mortality, CRT-D appeared to be superior to CRT-P, but a direct comparison between 2 devices was not performed.² In the extended follow-up observation of patients enrolled for the REsynchronization reVERses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study,⁴ compared with CRT-P, CRT-D significantly decreased the risk of death in patients with asymptomatic-to-mild heart failure (NYHA Class I or II) who had an LVEF of ≤40% and a QRS interval of ≥120 ms more.⁴ In contrast, advanced

	CRT-D (n=620)	CRT-P (n=97)	P value
Antiarrhythmic drugs			
Class Ia	5 (0.8)	2 (2.1)	0.242
Class Ib	14 (2.3)	2 (2.1)	0.903
Class Ic	5 (0.8)	2 (2.1)	0.242
Class III	199 (32.1)	18 (18.6)	0.0069
β -blockers	477 (76.9)	60 (61.9)	0.0014
Ca ²⁺ antagonists	53 (8.5)	13 (13.4)	0.124
Digitalis	83 (13.4)	17 (17.5)	0.274
Diuretics	499 (80.5)	74 (76.3)	0.338
ACEI or ARB	413 (66.6)	55 (56.7)	0.0566
Aldosterone antagonists	277 (44.7)	29 (29.9)	0.0062
Nitrates	73 (11.8)	13 (13.4)	0.646
Statins	192 (31.0)	22 (22.7)	0.0972
Oral anticoagulant agents	325 (52.4)	44 (45.4)	0.196
Antiplatelet agents	241 (38.9)	28 (28.9)	0.0584

Data are given as n (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker. Other abbreviations as in Table 1.

heart failure patients enrolled in the Management of Atrial fibrillation Suppression in AF-HF Comorbidity Therapy (MOSCOT) study showed similar survival rates with CRT-D vs. CRT-P during the 12-month follow-up period.⁵ Together, these studies indicate that there are likely to be small differences, if any, between heart failure patients with no prior sustained ventricular tachyarrhythmias (i.e., primary prevention) receiving CRT-D and CRT-P with regard to mortality or the rate of hospitalization for heart failure.

The aim of the present study was to clarify the effect of CRT-D and CRT-P for primary prevention on morbidity and mortality in patients with heart failure based on data from the Japan Cardiac Device Treatment Registry (JCDTR).

Methods

Study Population

The JCDTR was established in 2006 by the Japanese Heart Rhythm Society (JHRS) for a survey of actual conditions in patients undergoing implantation of cardiac implantable electronic devices (ICD, CRT-D, CRT-P), as described previously.⁶⁻⁸ This database is maintained on a voluntary basis by members of the JHRS under a unified protocol (https://center6.umin.ac.jp/islet/icd/plan_version_1_20090730.pdf), which is normally approved by each participating facility. As of 13 January 2017, 378 medical facilities in Japan had registered their data with the JCDTR. All members are encouraged to submit patient data at the time of implantation, as well as events related mortality and ICD therapy during the follow-up period, via the web page using a University hospital Medical Information Network (UMIN) server (<https://center6.umin.ac.jp/islet/icd/index.htm>). Details regarding data at the time of implantation have been reported previously.⁹ Of all patients receiving devices for primary prevention (2714 CRT-D, 555 CRT-P) with an implantation date between January 2011 and August 2015, follow-up data were available for 717 patients (620 CRT-D, 97 CRT-P) as of 16 September 2015. These 717 patients were included in the present study.

Outcomes

The events analyzed were in the present study: (1) death from any cause; (2) death from any cause or heart failure hospitalization, whichever came first; (3) heart failure death; and (4) sudden cardiac death. Diagnoses of heart failure were made and causes of death were ascertained by attending physicians.

Statistical Analyses

All data are expressed as the mean $\pm$ SD. Simple between-group analyses were conducted using Student's *t*-tests. Categorical variables were compared using Fisher's exact test. Logistic regression analysis was used to estimate the factors affecting the choice of CRT-D vs. CRT-P.

Figure 2. Kaplan-Meier estimates for event-free survival in patients with no prior sustained ventricular tachyarrhythmias and receiving a CRT-D or CRT-P. Outcome events were (A) death from any cause, (B) death or heart failure hospitalization (whichever came first), (C) heart failure death, and (D) SCD. (A) The rate of death from any cause at 12 and 24 months was 11% and 18%, respectively, in the CRT-D group, compared with 15% and 26% in the CRT-P group ($P=0.186$, log-rank test). (B) The rate of death or heart failure hospitalization at 12 and 24 months was 14% and 22%, respectively, in the CRT-D group, compared with 21% and 42% in the CRT-P group ($P=0.001$). (C) The rate of heart failure death at 12 and 24 months was 5% and 8%, respectively, in the CRT-D group, compared with 9% and 13% in the CRT-P group ($P=0.193$). (D) The rate of SCD at 12 and 24 months was 1.3% and 2.7%, respectively, in the CRT-D group, compared with 2.4% and 5.6% in the CRT-P group ($P=0.178$). Abbreviations as in Figure 1.

Kaplan-Meier curves were constructed to estimate event-free outcomes in the 2 study groups with comparisons using the log-rank test. Cox proportional-hazards regression model was used to estimate hazard ratios for clinical events. All covariates that reached a significance level of $P<0.1$ were then included in a multivariate regression model. To minimize the indication bias for device implantation, propensity score analyses were also conducted. The propensity score was calculated with the Cox proportional-hazards regression model using the following variables: age; sex; etiology (ischemic vs. non-ischemic); NYHA class; LVEF; QRS duration; history of atrial fibrillation (AF) and hypertension; hemoglobin; and treatment with β -blockers, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), aldosterone antagonists, and Class III anti-arrhythmic drugs. Two-sided $P<0.05$ was considered significant. Statistical analyses were performed using Statview version 5.0 for Windows (SAS Institute, Cary, NC, USA) or R software ver.3.2.3 (<https://www.r-project.org/>).

Results

Patient Characteristics

The characteristics of patients receiving CRT-D ($n=620$)

and CRT-P ($n=97$) devices for primary prevention are given in **Table 1**. Age and LVEF were significantly lower in the CRT-D than CRT-P group. Although a previous study reported significant prolongation of QRS duration in CRT-P recipients,⁹ there was no significant difference in QRS duration between the CRT-D than CRT-P groups in the present study. Male sex was prevalent in both groups, but its predominance was higher in patients with CRT-D. Patients receiving CRT-D were more likely to have a history of non-sustained ventricular tachycardia (NSVT). In contrast, they were less likely to have a history of hypertension. The distribution of NYHA functional classes and underlying heart diseases (ischemic vs. non-ischemic) did not differ significantly between the 2 groups, despite a trend for increased ischemic etiology in the CRT-D group. The Goldenberg risk score¹⁰ was lower in the CRT-D than CRT-P group.

Pharmacological therapy in the CRT-D and CRT-P groups is detailed in **Table 2**. The use of β -blockers, Class III anti-arrhythmic drugs, and aldosterone antagonists was significantly higher in the CRT-D group. There was a trend for higher use of ACEI or ARB and oral anticoagulant agents in the CRT-D than CRT-P group.

Among the clinical variables listed in **Table 1**, univariate logistic regression analyses identified 6 factors that were

Table 3. Hazard Ratios for Events in Patients Implanted With a CRT-D vs. CRT-P

Event	Hazard ratio	95% CI	P value
Death from any cause			
Unadjusted analysis	0.73	0.46–1.17	0.188
Adjusted analysis	0.97	0.59–1.60	0.897
Death or heart failure hospitalization			
Unadjusted analysis	0.54	0.37–0.78	0.0014
Adjusted analysis	0.72	0.47–1.10	0.125
Heart failure death			
Unadjusted analysis	0.65	0.34–1.25	0.196
Adjusted analysis	0.67	0.33–1.37	0.267
Sudden cardiac death			
Unadjusted analysis	0.47	0.16–1.44	0.188
Adjusted analysis	0.50	0.15–1.68	0.259

Models were adjusted for the following covariates: age at enrollment; underlying heart disease (ischemic vs. non-ischemic); NYHA class; hemoglobin; history of hypertension; and the use of Class III anti-arrhythmic drugs and ACEIs and/or ARBs. Covariates were identified from univariate Cox regression analyses ($P<0.1$). CI, confidence interval. Other abbreviations as in Tables 1,2.

Figure 3. Forest plots showing unadjusted hazard ratios of CRT-D vs. CRT-P for death or heart failure hospitalization (whichever came first) in different subgroups of CRT-D and CRT-P recipients. NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; AF, atrial fibrillation; NSVT, non-sustained ventricular tachycardia. Other abbreviations as in Figure 1.

associated with CRT-D vs. CRT-P implantation, namely age ($P<0.0001$), sex ($P=0.001$), LVEF ($P<0.0001$), hemoglobin ($P=0.025$), and a history of hypertension ($P=0.0041$) and NSVT ($P=0.0045$). In the multivariate analysis, age (odds ratio [OR] 0.91, 95% confidence interval [CI] 0.85–0.98; $P=0.012$) and a history of NSVT (OR 5.38, 95% CI 1.54–18.87; $P=0.0085$) were independent variables associated with the choice of CRT-D vs. CRT-P.

Outcomes

Over a mean follow-up of 21 ± 12 months, death or heart failure hospitalization occurred in 134 of 620 patients (21.6%) in the CRT-D group and in 33 of 97 patients

(34.0%) in the CRT-P group. In this group, death from any cause occurred in 114 CRT-D patients (18.4%) and in 21 CRT-P patients (21.6%). These events included 53 heart failure deaths (8.5%) and 14 sudden cardiac deaths (2.3%) in the CRT-D group and 11 heart failure deaths (11.3%) and 4 sudden cardiac deaths (4.1%) in the CRT-P group. The mode of death did not differ between the 2 groups ($P=0.48$; **Figure 1**). The incidence of cardiac death (i.e., heart failure and sudden cardiac death) was 59% in the CRT-D group and 71% in the CRT-P group.

The characteristics of the 4 patients with sudden cardiac death in the CRT-P group are summarized in **Table S1**. The rate of use of guideline-determined medical therapy, including β -blockers, ACEI/ARB, and aldosterone antagonists, was low in these patients. However, none of them had a history of hospital admission for heart failure after CRT-P implantation. Among the 14 CRT-D sudden cardiac deaths, 4 patients (29%) had prior appropriate ICD therapy. The appropriate ICD therapy and sudden death occurred on the same day in 2 patients. In the remaining 2 patients, sudden death occurred within 2 months of the appropriate ICD therapy in the absence of heart failure hospitalization.

Kaplan-Meier estimates of event-free survival in the 2 groups are shown in **Figure 2**. With regard to death or heart failure hospitalization (**Figure 2B**), the curves diverge at approximately 12 months and continue to separate thereafter ($P=0.0011$).

Hazard ratios for death from any cause, death or heart failure hospitalization, heart failure death, and sudden cardiac death are presented in **Table 3**. The unadjusted hazard ratio of 0.54 would indicate that there was a 46% reduction in the risk of death or heart failure hospitalization (whichever came first) among patients in the CRT-D group compared with those in the CRT-P group. However, there was no significant difference between the 2 groups with regard to the events mentioned above after adjustment for covariates. Conversely, the adjusted hazard ratio for heart failure hospitalization was 0.41 (95% CI 0.19–0.89; $P=0.024$) in the CRT-D group compared with the CRT-P group.

Forest plots of unadjusted hazard ratios of CRT-D vs. CRT-P for death or heart failure hospitalization by different subgroups are shown in **Figure 3**. Two marginal inter-

Table 4. Hazard Ratios for Events in Patients Implanted With a CRT-D vs. CRT-P After Propensity Score Matching

Event	Hazard ratio	95% CI	P value
Death from any cause	0.58	0.23–1.48	0.257
Death or heart failure hospitalization	0.63	0.28–1.38	0.244
Heart failure death	0.38	0.10–1.41	0.147
Sudden cardiac death ^A	NA	NA	NA

^ASudden cardiac death occurred in 3 of 166 patients within the propensity-matched cohort. All of these patients were recipients of a CRT-P, and so statistical analyses were not applicable. NA, not applicable. Other abbreviations as in Tables 1–3.

action effects, albeit lacking statistical significance, between subgroup and treatment were identified: (1) CRT-D was associated with a greater benefit in patients with LVEF $\leq 30\%$ (hazard ratio 0.41; 95% CI 0.25–0.68) than in those with LVEF $>30\%$ (hazard ratio 0.75; 95% CI 0.41–1.37; $P_{\text{interaction}}=0.090$); and (2) CRT-D was associated with a greater benefit in patients with NSVT (hazard ratio 0.27; 95% CI 0.065–1.15) than in those without NSVT (hazard ratio 1.58; 95% CI 0.21–12.15; $P_{\text{interaction}}=0.11$).

After propensity score matching, the study cohorts consisted of 83 CRT-D vs. 83 CRT-P patients (Table S2). Hazard ratios for all events with CRT-D vs. CRT-P tended to be lower, but they did not reach statistical significance (Table 4).

Discussion

In the present study, analysis of the JCDTR database demonstrated that heart failure patients receiving CRT-D had better outcomes in terms of a lower incidence of combined events of death or heart failure hospitalization than those receiving CRT-P for primary prevention. However, after adjustment for covariates, the better outcomes in patients with CRT-D vs. CRT-P were no longer significant. CRT-P recipients were less likely to be taking medications such as β -blockers, ACEI/ARB, and aldosterone antagonists than CRT-D recipients in the JCDTR.

The efficacy of ICD implantation for primary prevention of sudden cardiac death has been conclusively demonstrated in patients with prior myocardial infarction and reduced LVEF ($\leq 35\%$ ¹¹ or $\leq 30\%$ ¹²), whereas reports regarding its efficacy in non-ischemic cardiomyopathy are conflicting.^{13–16} Men were more likely to experience ventricular tachyarrhythmia episodes than women among patients with coronary artery disease and an ICD.¹⁷ In agreement, the benefits of ICD in heart failure patients with CRT were reported to be greater for patients with an ischemic etiology of cardiomyopathy and in males.^{18–20} In addition, patients with low (0–2) Goldenberg risk scores, which would indicate less comorbidity and a younger age, appeared to receive a substantial benefit from a defibrillator.²¹ In a retrospective observational study, CRT-D recipients aged ≥ 75 years did not have lower mortality than CRT-P recipients after adjusting for possible confounders.²² Further studies are required to determine which patients with no prior sustained ventricular tachyarrhythmias will benefit from a defibrillator in CRT, and there may be a need for randomized studies, especially in non-ischemic cardiomyopathy, to elucidate optimal CRT device selection.

In the COMPANION study,² CRT-D implantation was associated with a 36% reduction in the risk of death from any cause (hazard ratio 0.64; 95% CI 0.48–0.86; $P=0.003$)

compared with pharmacologic therapy, whereas CRT-P implantation was associated with a marginally significant reduction (24%) in risk (hazard ratio 0.76; 95% CI 0.58–1.01; $P=0.059$). This indicated the superiority of CRT-D over CRT-P in terms of the mortality benefit, but the magnitude of this benefit appeared to be small.

The present study did not demonstrate a significant reduction in risk of death with CRT-D over CRT-P. There could be several reasons that explain this observation. First, the mean follow-up duration of 21 months was relatively short. A review of controlled trials suggested that some of the superior effects of CRT-D over CRT-P, such as on all-cause mortality, manifested after a longer follow-up period (i.e., >1 year).²³ Second, the proportion of patients with a history of NSVT in the present study was higher in the CRT-D than CRT-P group, and we were not able to adjust for this difference. A subanalysis of Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) reported that rapid NSVTs indicated a 4.3-fold increase in the risk of appropriate ICD shocks in patients with mild-to-moderate heart failure and LVEF of $\leq 35\%$.²⁴ Furthermore, the presence of rapid NSVTs was independently associated with all-cause mortality.²⁴ Third, non-ischemic etiology was prevalent, especially in patients receiving CRT-P, in the present study, although it was not statistically significant (Table 1). The DANISH trial (Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality) demonstrated that the addition of ICD function fails to prolong survival in symptomatic heart failure patients with non-ischemic cardiomyopathy who have an LVEF of $\leq 35\%$.¹⁵ Recently, in an observational cohort study in Europe, non-ischemic patients with indications for CRT did not benefit from additional primary prevention ICD therapy, as opposed to ischemic patients.²⁵ This may be related to the facts that: (1) CRT offers a more favorable response with regard to reverse LV remodeling in cases of non-ischemic cardiomyopathy; and (2) the substrate for ventricular arrhythmias in ischemic cardiomyopathy appears to be more severe compared with a non-ischemic etiology.²⁶

Although the effect of CRT on heart failure would be the same in both groups, a composite endpoint of death or heart failure hospitalization was reduced in the CRT-D compared with CRT-P group. This may be because: (1) the proportion of patients receiving β -blockers and aldosterone antagonists was significantly lower in the CRT-P than CRT-D group (Table 2); and (2) CRT-P recipients had more comorbidities, as determined using the Goldenberg risk score (Table 1). More intensive medical therapy with β -blockers,^{27–29} ACEI/ARB,^{30–33} and aldosterone antagonists^{34,35} may have improved outcomes of death or heart failure hospitalization in patients receiving CRT-P. In

addition, patients with CRT-D are likely to be under remote monitoring because of a defibrillator. In a randomized control study,³⁶ as well as in observational studies,^{37,38} remote monitoring was associated with a lower rate of hospital admission for heart failure or all-cause mortality.

The rate of sudden cardiac death tended to be lower in the CRT-D than CRT-P group, but the difference between the 2 groups did not reach statistical significance. This appears to be due to the low proportion of sudden cardiac deaths in heart failure patients treated with guideline-determined medical therapy and CRT. For example, the rate of sudden cardiac death was 1.18% and 1.08% per patient years in CRT-P recipients in the Certitude cohort³⁹ and REVERSE⁴ studies, respectively. In these studies, the incidence of sudden cardiac death was not significantly higher in the CRT-P compared with CRT-D group. Moreover, first ICD shock efficacy in the MADIT-CRT study was approximately 90%,⁴⁰ and the rate of successful conversion of spontaneous ventricular arrhythmias at the final ICD therapy was reported to be 97.3%.⁴¹ Such failed ICD therapies may be due to the presence of patients with a high defibrillation threshold,⁴² undersensing of ventricular fibrillation,⁴³ and device malfunction.⁴³ In addition, Holter electrocardiogram (ECG) monitoring revealed that approximately 20% of patients had bradyarrhythmias during sudden cardiac death,^{44,45} and some of these could be pulseless electrical activity. In fact, the rate of sudden cardiac death in the CRT-D group in the COMPANION study was 2.9% during the 15.7-month follow-up period,⁴⁶ which is comparable to the 2.7% rate at 2 years in the present study (Figure 2D).

The results of the preset study suggest that there are 2 subgroups that will gain a larger benefit from a defibrillator: (1) patients with a reduced LVEF ($\leq 30\%$); and (2) patients with NSVT (Figure 3). Conversely, care should be taken when interpreting the results based on unadjusted analyses. In addition, data concerning the history of NSVT was missing for 60% ($n=433$) of patients (Table 1). This shortcoming is related to the data entry system of the JCDTR, where entering information as to the presence or absence of NSVT is not mandatory to finish registration.

Study Limitations

There are several limitations to be considered in the present study. First, the JCDTR database relies on voluntary efforts of members of the JHRS, and would not include all data for consecutive patients in each hospital. However, more than 378 facilities across Japan have contributed to the registry, which means that the data could be representative of the outcomes of patients with CRT in Japan. Second, although the present study presented outcomes of patients who underwent CRT-D ($n=620$) or CRT-P ($n=97$) implantation for primary prevention from the entire cohort (2714 CRT-D, 555 CRT-P) reported previously,⁹ the number of patients in the 2 groups in the present study suggests that follow-up data are not easily obtained from the JCDTR, being available for only 23% of the CRT-D group and 17% of the CRT-P group. Conversely, the characteristics of the patients in the present study (Tables 1,2) were almost identical to those reported in the previous study.⁹ Third, the number of patients (especially CRT-P recipients) was relatively small for adjusting large differences in the background and medications of the 2 study groups (CRT-D vs. CRT-P). Fourth, the present study was limited by a lack of important data, such as the rate of

responders and the morphology of the original QRS complex (left bundle block or right bundle block). In general, the effect of CRT was equal in both groups.

Conclusions

The present study demonstrated that patients with CRT-D for primary prevention enrolled in the JCDTR had a lower rate of death or heart failure hospitalization during a mean follow-up of 21 months than patients with CRT-P. There was a tendency for lower rates of death from any cause, death or heart failure hospitalization, heart failure death, and sudden cardiac death, in patients with CRT-D compared with CRT-P, although the differences failed to reach statistical significance.

Acknowledgments

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Conflicts of Interest

All authors declare no conflicts of interest related to this study.

References

1. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002; **346**: 1845–1853.
2. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004; **350**: 2140–2150.
3. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005; **352**: 1539–1549.
4. Gold MR, Daubert JC, Abraham WT, Hassager C, Dinerman JL, Hudnall JH, et al. Implantable defibrillators improve survival in patients with mildly symptomatic heart failure receiving cardiac resynchronization therapy: Analysis of the long-term follow-up of remodeling in systolic left ventricular dysfunction (reverse). *Circ Arrhythm Electrophysiol* 2013; **6**: 1163–1168.
5. Schuchert A, Muto C, Maounis T, Frank R, Boulogne E, Polauck A, et al. Lead complications, device infections, and clinical outcomes in the first year after implantation of cardiac resynchronization therapy-defibrillator and cardiac resynchronization therapy-pacemaker. *Europace* 2013; **15**: 71–76.
6. Shimizu A, Mitsuhashi T, Furushima H, Sekiguchi Y, Manaka T, Nishii N, et al. Current status of cardiac resynchronization therapy with defibrillators and factors influencing its prognosis in Japan. *J Arrhythm* 2013; **29**: 168–174.
7. Shimizu A, Nitta T, Kurita T, Imai K, Kimura T, Kobayashi Y, et al. Current status of implantable defibrillator devices in patients with left ventricular dysfunction: The first report from the online registry database. *J Arrhythm* 2008; **24**: 133–140.
8. Shimizu A, Nitta T, Kurita T, Imai K, Kobayashi Y, Soejima K, et al. Actual conditions of implantable defibrillator therapy over 5 years in Japan. *J Arrhythm* 2012; **28**: 263–272.
9. Yokoshibi H, Shimizu A, Mitsuhashi T, Furushima H, Sekiguchi Y, Manaka T, et al. Trends and determinant factors in the use of cardiac resynchronization therapy devices in Japan: Analysis of the Japan Cardiac Device Treatment Registry database. *J Arrhythm* 2016; **32**: 486–490.
10. Goldenberg I, Vyas AK, Hall WJ, Moss AJ, Wang H, He H, et al. Risk stratification for primary implantation of a cardioverter-defibrillator in patients with ischemic left ventricular dysfunction. *J Am Coll Cardiol* 2008; **51**: 288–296.
11. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia: Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996; **335**: 1933–1940.

12. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002; **346**: 877–883.
13. Bansch D, Antz M, Boczor S, Volkmer M, Tebbenjohanns J, Seidl K, et al. Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: The Cardiomyopathy Trial (CAT). *Circulation* 2002; **105**: 1453–1458.
14. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med* 2004; **350**: 2151–2158.
15. Kober L, Thune JJ, Nielsen JC, Haarto J, Videbaek L, Korup E, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med* 2016; **375**: 1221–1230.
16. Strickberger SA, Hummel JD, Bartlett TG, Frumin HI, Schuger CD, Beau SL, et al. Amiodarone versus implantable cardioverter-defibrillator: Randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia – AMIOVIRT. *J Am Coll Cardiol* 2003; **41**: 1707–1712.
17. Lampert R, McPherson CA, Clancy JF, Caulin-Glaser TL, Rosenfeld LE, Batsford WP. Gender differences in ventricular arrhythmia recurrence in patients with coronary artery disease and implantable cardioverter-defibrillators. *J Am Coll Cardiol* 2004; **43**: 2293–2299.
18. Barra S, Providencia R, Tang A, Heck P, Virdee M, Agarwal S. Importance of implantable cardioverter-defibrillator back-up in cardiac resynchronization therapy recipients: A systematic review and meta-analysis. *J Am Heart Assoc* 2015; **4**: e002539.
19. Kutyla V, Geller L, Bogyi P, Zima E, Aktas MK, Ozcan EE, et al. Effect of cardiac resynchronization therapy with implantable cardioverter defibrillator versus cardiac resynchronization therapy with pacemaker on mortality in heart failure patients: Results of a high-volume, single-centre experience. *European J Heart Fail* 2014; **16**: 1323–1330.
20. Witt CT, Kronborg MB, Nohr EA, Mortensen PT, Gerdes C, Jensen HK, et al. Adding the implantable cardioverter-defibrillator to cardiac resynchronization therapy is associated with improved long-term survival in ischaemic, but not in non-ischaemic cardiomyopathy. *Europace* 2016; **18**: 413–419.
21. Barra S, Looi KL, Gajendragadkar PR, Khan FZ, Virdee M, Agarwal S. Applicability of a risk score for prediction of the long-term benefit of the implantable cardioverter defibrillator in patients receiving cardiac resynchronization therapy. *Europace* 2016; **18**: 1187–1193.
22. Munir MB, Althouse AD, Rijal S, Shah MB, Abu Daya H, Adelstein E, et al. Clinical characteristics and outcomes of older cardiac resynchronization therapy recipients using a pacemaker versus a defibrillator. *J Cardiovasc Electrophysiol* 2016; **27**: 730–734.
23. Jiang M, He B, Zhang Q. Comparison of CRT and CRT-D in heart failure: Systematic review of controlled trials. *Int J Cardiol* 2012; **158**: 39–45.
24. Chen J, Johnson G, Hellkamp AS, Anderson J, Mark DB, Lee KL, et al. Rapid-rate nonsustained ventricular tachycardia found on implantable cardioverter-defibrillator interrogation: Relationship to outcomes in the SCD-HEFT (Sudden Cardiac Death In Heart Failure Trial). *J Am Coll Cardiol* 2013; **61**: 2161–2168.
25. Barra S, Boveda S, Providencia R, Sadoul N, Duehmke R, Reitan C, et al. Adding defibrillation therapy to cardiac resynchronization on the basis of the myocardial substrate. *J Am Coll Cardiol* 2017; **69**: 1669–1678.
26. Yokoshiki H, Mitsuyama H, Watanabe M, Mitsuhashi T, Shimizu A. Cardiac resynchronization therapy in ischemic and non-ischemic cardiomyopathy. *J Arrhythm*, doi:10.1016/j.joa.2017.03.002.
27. Effect of metoprolol cr/rl in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999; **353**: 2001–2007.
28. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): A randomised trial. *Lancet* 1999; **353**: 9–13.
29. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure: U.S. Carvedilol Heart Failure Study Group. *N Engl J Med* 1996; **334**: 1349–1355.
30. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: Results of the Cooperative North Scandinavian Enalapril Survival Study (Consensus). *N Engl J Med* 1987; **316**: 1429–1435.
31. SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991; **325**: 293–302.
32. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: The CHARM-Alternative trial. *Lancet* 2003; **362**: 772–776.
33. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: The CHARM-Added trial. *Lancet* 2003; **362**: 767–771.
34. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; **348**: 1309–1321.
35. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure: Randomized aldactone evaluation study investigators. *N Engl J Med* 1999; **341**: 709–717.
36. Hindricks G, Taborsky M, Glikson M, Heinrich U, Schumacher B, Katz A, et al. Implant-based multiparameter telemonitoring of patients with heart failure (in-time): A randomised controlled trial. *Lancet* 2014; **384**: 583–590.
37. De Simone A, Leoni L, Luzi M, Amellone C, Stabile G, La Rocca V, et al. Remote monitoring improves outcome after ICD implantation: The clinical efficacy in the management of heart failure (EFFECT) study. *Europace* 2015; **17**: 1267–1275.
38. Saxon LA, Hayes DL, Gilliam FR, Heidenreich PA, Day J, Seth M, et al. Long-term outcome after ICD and CRT implantation and influence of remote device follow-up: The ALTITUDE survival study. *Circulation* 2010; **122**: 2359–2367.
39. Marijon E, Leclercq C, Narayanan K, Boveda S, Klug D, Lacaze-Gadonneix J, et al. Causes-of-death analysis of patients with cardiac resynchronization therapy: An analysis of the CeRTiTuDe cohort study. *Eur Heart J* 2015; **36**: 2767–2776.
40. Kutyla V, Huth Ruwald AC, Aktas MK, Jons C, McNitt S, Polonsky B, et al. Clinical impact, safety, and efficacy of single-versus dual-coil ICD leads in MADIT-CRT. *J Cardiovasc Electrophysiol* 2013; **24**: 1246–1252.
41. Gold MR, Higgins S, Klein R, Gilliam FR, Kopelman H, Hessen S, et al. Efficacy and temporal stability of reduced safety margins for ventricular defibrillation: Primary results from the low energy safety study (LESS). *Circulation* 2002; **105**: 2043–2048.
42. Mizukami K, Yokoshiki H, Mitsuyama H, Watanabe M, Tenma T, Matsui Y, et al. Predictors of high defibrillation threshold in patients with implantable cardioverter-defibrillator using a transvenous dual-coil lead. *Circ J* 2015; **79**: 77–84.
43. Tseng ZH, Hayward RM, Clark NM, Mulvanny CG, Colburn BJ, Ursell PC, et al. Sudden death in patients with cardiac implantable electronic devices. *JAMA Intern Med* 2015; **175**: 1342–1350.
44. Bayes de Luna A, Coumel P, Leclercq JF. Ambulatory sudden cardiac death: Mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. *Am Heart J* 1989; **117**: 151–159.
45. Watanabe E, Tanabe T, Osaka M, Chishaki A, Takase B, Niwano S, et al. Sudden cardiac arrest recorded during holter monitoring: Prevalence, antecedent electrical events, and outcomes. *Heart Rhythm* 2014; **11**: 1418–1425.
46. Carson P, Anand I, O'Connor C, Jaski B, Steinberg J, Lwin A, et al. Mode of death in advanced heart failure: The comparison of medical, pacing, and defibrillation therapies in heart failure (COMPANION) trial. *J Am Coll Cardiol* 2005; **46**: 2329–2334.

Appendix

Facilities (in alphabetical order) that have enrolled more than 100 patients in the JCDTR as of 13 January 2017:

Akita Medical Center; Anjo Kosei Hospital; Dokkyo Medical University; Edogawa Hospital; Fujita Health University; Fukushima Medical University; Gifu University; Gunma University; Hirosaki University; Hokkaido University Hospital; Hokko Memorial Hospital; Hyogo College of Medicine; IMS Katsushika Heart Center; Ishinomaki Red Cross Hospital; Itabashi Chuo Medical Center; Japanese Red Cross Society Kyoto Daini Hospital; Japanese Red Cross Wakayama Medical Center; JCHO Hokkaido Hospital; JCHO Kyushu Hospital; Jichi Medical University; Juntendo University; Juntendo University Urayasu Hospital; Kakogawa East City Hospital; Kameda Medical Center; Kanazawa Medical University; Keio University; Kitasato

University; Kochi Health Science Center; Kokura Memorial Hospital; Komaki City Hospital; Kumamoto Red Cross Hospital; Kumamoto University; Kurashiki Chuo Hospital; Kyorin University; Kyoto Prefectural University of Medicine; Kyoto-Katsura Hospital; Maebashi Red Cross Hospital; Matsudo City Hospital; Matsue Red Cross Hospital; Matsumoto Kyoritsu Hospital; Mie University; Mito Saiseikai General Hospital; Nagasaki University; Nagoya University; Nara Medical University; National Hospital Organization Kagoshima Medical Center; National Hospital Organization Shizuoka Medical Center; Nihon University; Niigata University; Nippon Medical School Chiba Hokusou Hospital; Nippon Medical University; Odawara Municipal Hospital; Okayama University; Okinawa Prefectural Chubu Hospital; Osaka City General Hospital; Osaka City University; Osaka Medical College; Osaka Police Hospital; Osaka Red Cross Hospital; Osaka University; Saiseikai Fukuoka General Hospital; Saiseikai Kumamoto Hospital; Saiseikai Shimonoseki General Hospital; Saiseikai Yokohamashi Tobu Hospital; Saitama Red Cross Hospital; Sakurabashi Watanabe Hospital; Seirei Hamamatsu General Hospital; Sendai Kosei Hospital; Shiga University of Medical Science; Shinshu University; Shizuoka municipal Hospital; Showa General Hospital; St. Luke's International Hospital; St. Marianna University School of Medicine; Takeda Hospital; Tenri Hospital; The

University of Tokyo; Toho University; Tokai University; Tokyo Medical University; Tokyo Metropolitan Hiroo Hospital; Tokyo Metropolitan Tama Medical Center; Tokyo Women's Medical University; Tottori University; Toyama Prefectural Central Hospital; Toyohashi Heart Center; Tsuchiura Kyodo General Hospital; Tsukuba Medical Center Hospital; University of Fukui; University of Miyazaki; University of Occupational and Environmental Health; University of Tsukuba; Yamagata Prefectural Central Hospital; Yamagata University; Yamaguchi University; Yamanashi Prefectural Central Hospital; Yokohama Rosai Hospital.

Supplementary Files

Supplementary File 1

Table S1. Characteristics and pharmacological therapy in 4 CRT-P recipients experiencing sudden cardiac death

Table S2. Patient characteristics and pharmacological therapy after propensity score matching

Please find supplementary file(s);
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