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ORIGINAL ARTICLE
Heart Failure

Recent Trends in Achievement Rates and Time Required for Left Ventricular Reverse Remodeling in Dilated Cardiomyopathy

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Background: Left ventricular reverse remodeling (LVRR) is associated with a good prognosis in patients with dilated cardiomyopathy (DCM), so in this study we examined the achievement rates of LVRR, the time taken to LVRR and the factors associated with LVRR in recent cases of DCM.

Methods and Results: We enrolled 121 patients with DCM. LVRR was defined as a left ventricular ejection fraction ≥40% at follow-up with a ≥10% improvement. LVRR was observed in 82 patients (68%). The median time to LVRR was 208 days. Multivariate analysis revealed that B-type natriuretic peptide (BNP) levels at discharge (per 1-SD increase, odds ratio: 0.483, 95% confidence interval (CI): 0.224–0.963; P=0.0385) and β-blocker dose (per 1-SD increase, odds ratio: 3.379, 95% CI: 1.644–7.702; P=0.0007) were independently associated with LVRR. When the patients were divided into 2 groups according to the first (2007–2017; n=64) and second (2018–2022; n=57) time periods, there was a significantly higher LVRR achievement rate (48.4% vs. 89.5%) and shorter time to LVRR in the second period than in the first.

Conclusions: The LVRR achievement rate in DCM has been increasing, and the time to LVRR has been shortened in recent years. Beta-blocker dose and BNP levels at discharge may be strongly associated with LVRR.

Key Words: B-type natriuretic peptide; Beta-blockers; Dilated cardiomyopathy; Left ventricular reverse remodeling

Dilated cardiomyopathy (DCM) is defined as the presence of global left ventricular (LV) systolic dysfunction and LV dilation in the absence of ischemic heart disease or secondary cardiomyopathy,[1–3] and is a major cause of heart failure with reduced ejection fraction (HFrEF). DCM is a progressive disease that leads to fatal arrhythmias and sudden death, and it is the most common reason for heart transplantation in Japan.[4] Although curative treatments for DCM have not yet been developed, the prognosis of patients with DCM has improved over the past 2 decades with advances in the treatment of HF.[5] LV reverse remodeling (LVRR) is associated with a particularly good prognosis in patients with DCM receiving optimal medical therapy.[6] In Japan, LVRR is achieved in 34–53% of patients with DCM.[7,8] Previous studies using personal clinical records reported that β-blockers and angiotensin-converting enzyme inhibitors (ACEi)/angiotensin II receptor blockers (ARBs) are effective for achieving LVRR in patients with DCM,[5,9] and recent guideline-directed medical therapy (GDMT) has

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been strongly recommended for HFrEF. New therapeutic agents for HF, such as angiotensin-receptor-neprilysin inhibitors (ARNI) and sodium–glucose cotransporter 2 inhibitors (SGLT2i), have become available in Japan,[10] which may further improve the prognosis of DCM. However, despite the many studies that have focused on HFrEF, there are few reports on recent LVRR achievement rates for DCM alone after the Japanese guidelines for HF were updated. Whether or not a patient achieves LVRR also affects the indication for primary preventive implantable cardioverter-defibrillator (ICD) therapy. Guidelines recommend a 3-month drug treatment period to determine the indication for ICD, but the PROLONG study showed that LVRR in HFrEF patients can occur beyond 3 months.[11] There are few reports on the time taken to achieve LVRR and temporal changes in DCM patients. The purpose of this study was to examine (1) the LVRR achievement rate, the time to LVRR in recent DCM cases and the temporal changes, and (2) the factors associated with LVRR.

Methods

Study Population

This study enrolled 144 patients with first-onset DCM who were admitted to Yamagata University Hospital between January 2007 and December 2022. DCM was diagnosed based on the definition provided in the Japanese Circulation Society Guidelines (i.e., LV dilatation and reduced LV ejection fraction [LVEF] in the absence of any of the following specific cardiac or systemic diseases and history: poorly controlled hypertension, severe valvular disease, history of heavy alcohol consumption, peripartum cardiomyopathy, myocarditis, neuromuscular diseases, connective tissue diseases, malnutrition or beriberi, metabolic diseases, amyloidosis, sarcoidosis, history of cardiotoxic drug use, history of tachycardia or tachycardia-induced cardiomyopathy, dilated-phase of hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and adult congenital heart disease).[12] LV dilatation and reduced LVEF were defined as LVEF <50% with an indexed LV end-diastolic internal diameter >33 mm/m^2 [men] or >32 mm/m^2 [women].[13] All of the study patients underwent myocardial biopsy or contrast-enhanced cardiac magnetic resonance imaging. Of the 144 patients, 27 underwent genetic testing via whole-exome sequencing as previously reported.[14] In order to examine the temporal changes in LVRR achievement rates and time to LVRR, patients were divided into 2 groups based on the median year of DCM diagnosis: 2007–2017 (n=75) and 2018–2022 (n=69). Patients who did not undergo follow-up echocardiography at 6 or 12 months after diagnosis were excluded, so the final analysis included 121 patients (first time period: n=64; second time period: n=57). The study complied with the principles of the Declaration of Helsinki, and all patients provided informed consent before participating in the study. The study protocol was approved by the institution's Human Investigations Committee (Approval No. 2019-78).

Clinical Data

Demographic and clinical data, including age, sex, duration of first hospitalization, medication use, and family history of cardiomyopathy, were obtained from patient interviews and medical records. Body mass index (BMI) was calculated from weight and height measurements by dividing weight (kg) by the square of the height (m^2). Hypertension was indicated by systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure ≥90 mmHg, and/or current use of antihypertensive drugs. BMI and SBP data were obtained at discharge during the initial hospitalization. Blood samples were obtained at admission and discharge during the initial hospitalization. B-type natriuretic peptide (BNP) levels were measured using a commercially available specific radioimmunoassay kit (SHIONORIA BNP assay kit; Shionogi & Co., Ltd., Osaka, Japan). The Modification of Diet in Renal Disease equation with the Japanese coefficient was used to calculate the estimated glomerular filtration rate (eGFR) using the serum creatinine value. The common logarithmic values of the BNP values and the duration of first hospitalization were used in the logistic regression analysis. Transthoracic echocardiography (TTE) was performed at baseline, then at 3, 6, and 12 months after diagnosis, and every 12 months thereafter whenever possible. The LV end-diastolic internal diameter (LVDd) was measured in the 2D-parasternal long-axis view, while LVEF was measured using the biplane modified Simpson's method in the apical 4- and 2-chamber views.

Dose of Drugs

Optimal medical therapy for HF was based on guidelines at diagnosis, and drug titration was performed at the discretion of the attending physician. Drug doses were evaluated at 3 month after discharge during the initial hospitalization. The dose of β-blocker was standardized using carvedilol units. The dose equivalents for carvedilol and bisoprolol were derived from the Japanese Circulation Society Guidelines on the Diagnosis and Treatment of Acute and Chronic Heart Failure.[15] In other words, 5 mg bisoprolol was equivalent to 20 mg carvedilol. The ACEi/ARB dose was expressed in enalapril equivalents. The maximum dose of each drug was equivalent to 10 mg enalapril.

Study Endpoint

The study endpoint was LVRR, defined as LVEF ≥40% at follow-up and ≥10% absolute improvement in the LVEF from baseline to follow-up on TTE.[16,17] Time to LVRR was defined as the number of days from the initiation of medication to the date when LVRR was confirmed. The change in LVEF (ΔLVEF) was defined using the following formula: ΔLVEF = maximum LVEF at follow-up − baseline LVEF.

Statistical Analysis

Categorical variables were analyzed using the chi-square test, and continuous variables were analyzed using a t-test for normally distributed variables or the Mann-Whitney U test for not normally distributed variables. Results are expressed as mean±standard deviation for normally distributed variables or median (interquartile range [IQR]) for not normally distributed variables. For continuous variables, differences between groups were assessed using analysis of variance (ANOVA) with Tukey's post hoc test. Logistic regression analysis was performed to identify the independent predictors of LVRR. Variables that were significant in the univariate logistic regression analysis ($P<0.05$) were entered into the multivariate analysis. All analyses were performed using JMP Pro software (version 17.0; SAS Institute Inc., Cary, NC, USA). For all tests, $P<0.05$ was considered significant.

Table 1. Characteristics of Patients With and Without LVRR

	All	LVRR (+) (n=82)	LVRR (–) (n=39)	P value
Age at diagnosis, years	55.8±14.0	55.9±14.1	55.5±14.1	0.9012
Male sex, n	36 (72%)	61 (75%)	31 (78%)	0.7905
BMI, kg/m^2	24.2±5.7	23.7±3.9	24.0±3.9	0.8309
SBP, mmHg	112±14	113±15	108±12	0.1943
Duration of hospitalization, days	23 (12–43)	28 (11–48)	17 (13–30)	0.2199
Family history of cardiomyopathy, n	8 (7%)	7 (9%)	1 (3%)	0.4284
Hypertension, n	47 (39%)	32 (39%)	15 (38%)	0.9527
Diabetes, n	43 (36%)	28 (34%)	15 (38%)	0.6430
Atrial fibrillation, n	30 (25%)	14 (17%)	16 (40%)	0.0065
Left bundle branch block, n	18 (15%)	15 (18%)	3 (8%)	0.1091
LVEF at baseline, %	27.7±8.2	32.4±7.3	31.0±8.0	0.3959
LVDd at baseline, mm	62.9±6.8	62.5±6.8	65.7±8.3	0.1688
BNP at admission, pg/mL	456 (145–824)	486 (157–862)	381 (123–627)	0.3187
BNP at discharge, pg/mL	81 (43–225)	78 (40–154)	283 (69–381)	0.0138
eGFR at discharge, mL/min/1.73 m^2	69.4±14.9	69.7±15.2	68.2±14.3	0.5949
Medications				
β-blocker, n	111 (96%)	80 (99%)	31 (89%)	0.0131
Carvedilol equivalent dose, mg/day	16.4±7.7	18.9±7.2	10.9±7.2	<0.0001
ACEi/ARB, n	109 (94%)	80 (99%)	29 (83%)	0.0010
Enalapril equivalent dose, mg/day	5.3±3.0	5.8±2.8	4.0±3.0	0.0048
ARNI, n	17 (14%)	15 (18%)	2 (5%)	0.0515
MRA, n	63 (54%)	44 (54%)	19 (54%)	0.9972
Loop diuretics, n	40 (34%)	22 (27%)	18 (51%)	0.0116
SGLT2i, n	16 (13%)	14 (17%)	2 (5%)	0.0699
PM/ICD/CRT, n	17 (14%)	12 (19%)	5 (9%)	0.1463

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNI, angiotensin-receptor-neprilysin inhibitor; BMI, body mass index; BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; LVDd, left ventricular end-diastolic internal diameter; LVEF, left ventricular ejection fraction; LVRR, left ventricular reverse remodeling; MRA, mineralocorticoid-receptor antagonist; PM, pacemaker; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

Results

Patients' Characteristics

The mean age of the patients at DCM diagnosis was 55.8±14.0 years (**Table 1**), and 72% were male. The median duration of the initial hospitalization was 23 days (IQR: 12–43 days). At the time of DCM diagnosis, 30 patients (25%) had atrial fibrillation (AF), and 18 patients (15%) had left bundle branch block (LBBB). The mean LVEF and LVDd at diagnosis were 27.7±8.2% (min–max, 11–46%) and 62.9±6.8 mm (min–max, 52–84 mm), respectively. The median BNP levels at admission and discharge were 456 pg/mL (IQR: 145–824 pg/mL) and 81 pg/mL (IQR: 43–225 pg/mL), respectively. LVRR occurred in 82 of the 121 patients (68%). There were no significant differences in age, sex, BMI, prevalence of hypertension and diabetes, LVEF at diagnosis, or eGFR between patients with and without LVRR. Patients with LVRR had a significantly lower prevalence of AF (17% vs. 40%, P=0.0065) and lower BNP levels at discharge (78 [40–154] pg/mL vs. 283 [69–381] pg/mL, P=0.0138). The LVRR group used β-blockers (99% vs. 89%, P=0.0131) and ACEi/ARB (99% vs. 83%, P<0.0001) more often than those without LVRR. Furthermore, the dose of these drugs were significantly higher in patients with LVRR (carvedilol equivalent dose, 18.9±7.2 mg/day vs. 10.9±7.2 mg/day, P<0.0001; enalapril equivalent dose, 5.8±2.8 mg/day vs. 4.0±3.0 mg/day, P=0.0048) than in those without. The use of loop diuretics was significantly lower in patients with LVRR than in those without LVRR (27% vs. 51%, P=0.0116), but the use of mineralocorticoid-receptor antagonists (MRA) was not significantly different between the 2 groups (54% vs. 54%, P=0.9972). The use of ARNI and SGLT2i tended to be higher in patients with LVRR than in those without LVRR, but the difference was not statistically significant.

Factors Affecting LVRR

To determine the factors affecting the achievement of LVRR, we performed univariate and multivariate logistic regression analyses (**Table 2**). In the univariate analysis, AF, logBNP levels at discharge, the prescription rate and dose of β-blockers, prescription rate and dose of ACEi/ARB/ARNI, and prescription rate of loop diuretics were significantly associated with LVRR. Multivariate analysis revealed that the level of logBNP at discharge (odds ratio: 0.483; 95% confidence interval (CI): 0.224–0.963; P=0.0385) and dose of β-blocker (odds ratio: 3.379; 95% CI: 1.644–7.702; P=0.0007) were independently associated with LVRR. As β-blocker dose increased, ΔLVEF also significantly increased (**Supplementary Figure 1**). In the receiver operating characteristic (ROC) analysis for predicting LVRR, the area under the curve (AUC) for β-blocker dose was 0.78, and the cutoff value was 15 mg/day of carvedilol (sensitivity, 0.78; specificity, 0.67) (**Figure 1A**).

Table 2. Logistic Regression Analysis for LVRR

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Age at diagnosis (per 1 year increase)	1.002	0.975–1.030	0.8748			
Male sex	0.930	0.365–2.241	0.8740			
BMI (per 1SD increase)	0.877	0.360–1.140	0.7256			
SBP (per 1SD increase)	1.438	0.845–2.566	0.1840			
Log duration of hospitalization (per 1SD increase)	1.238	0.767–2.003	0.3780			
Family history of cardiomyopathy	2.333	0.383–44.92	0.3984			
Hypertension	1.024	0.470–2.269	0.9526			
Diabetes	0.830	0.378–1.849	0.6440			
Atrial fibrillation	0.358	0.151–0.842	0.0187	0.645	0.167–2.725	0.5367
Left bundle branch block	2.687	0.819–12.14	0.1076			
LVEF at diagnosis (per 1SD increase)	1.288	0.848–1.975	0.2343			
LVDd at diagnosis (per 1SD increase)	0.643	0.333–1.215	0.1716			
Log BNP at admission (per 1SD increase)	1.350	0.776–2.350	0.2837			
Log BNP at discharge (per 1SD increase)	0.358	0.191–0.623	0.0002	0.483	0.224–0.963	0.0385
eGFR at discharge (per 1SD increase)	1.120	0.745–1.716	0.5893			
β-blocker	9.257	1.312–184.5	0.0245			
Carvedilol equivalent dose (per 1SD increase)	4.400	2.522–8.352	<0.0001	3.379	1.644–7.702	0.0007
ACEi/ARB	14.73	2.391–283.7	0.0024	6.424	0.725–143.2	0.0978
Enalapril equivalent dose (per 1SD increase)	1.966	1.230–3.302	0.0038			
ARNI	4.141	1.089–27.19	0.0357			
MRA	1.042	0.482–2.242	0.9152			
Loop diuretics	0.352	0.153–0.800	0.0127	0.459	0.121–1.693	0.2392
SGLT2i	3.809	0.993–25.09	0.0514			
PM/ICD/CRT	2.471	0.746–11.22	0.1463			

CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

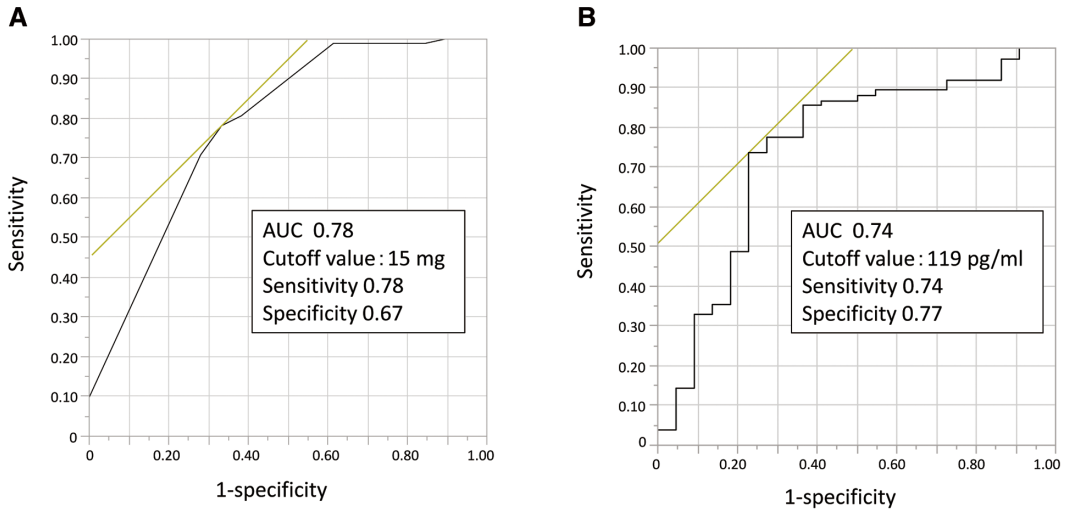

Figure 1. Receiver operating characteristic (ROC) analysis for predicting LVRR. The area under the curve (AUC) and cutoff value of β-blocker dose (**A**) and level of BNP at discharge (**B**) were 0.78 and 15 mg/day of carvedilol (sensitivity, 0.78; specificity, 0.67), 0.74 and 119 pg/mL (sensitivity, 0.74; specificity, 0.77), respectively. BNP, B-type natriuretic peptide; LVRR, left ventricular reverse remodeling.

Table 3. Comparison of Patient Characteristics in the First and Second Periods

	First time period (2007–2017) (n=64)	Second time period (2018–2022) (n=57)	P value
Age at diagnosis, years	56.0±14.2	56.2±14.4	0.5308
Male sex, n	56 (81%)	41 (71%)	0.4411
BMI, kg/m^2	24.2±4.7	23.1±4.2	0.6427
SBP, mmHg	113±14	112±15	0.5570
Duration of hospitalization, days	24 (11–43)	23 (12–44)	0.8988
Family history of cardiomyopathy, n	3 (5%)	5 (9%)	0.9736
Hypertension, n	22 (34%)	25 (44%)	0.2853
Diabetes, n	26 (41%)	17 (30%)	0.2153
Atrial fibrillation, n	19 (30%)	11 (19%)	0.1865
Left bundle branch block, n	13 (20%)	5 (9%)	0.0750
LVEF at diagnosis, %	29.6±8.4	26.4±8.0	0.0866
LVDd at diagnosis, mm	64.7±8.1	62.3±6.2	0.2132
BNP at admission, pg/mL	379 (130–667)	460 (183–867)	0.3320
BNP at discharge, pg/mL	116 (53–281)	70 (40–212)	0.3431
eGFR at discharge, mL/min/1.73 m^2	69.9±12.7	68.8±16.9	0.7175
Medications			
β-blocker, n	56 (95%)	55 (96%)	0.6761
Carvedilol equivalent dose, mg/day	14.1±6.5	18.9±8.8	0.0010
ACEi/ARB, n	53 (90%)	56 (98%)	0.0571
Enalapril equivalent dose, mg/day	5.0±3.0	5.5±3.0	0.3547
ARNI, n	1 (2%)	16 (28%)	<0.0001
MRA, n	29 (44%)	37 (65%)	0.0243
Loop diuretic, n	28 (47%)	12 (21%)	0.0028
SGLT2i, n	1 (2%)	15 (26%)	<0.0001
PM/ICD/CRT, n	12 (19%)	5 (9%)	0.1149

Abbreviations as in Table 1.

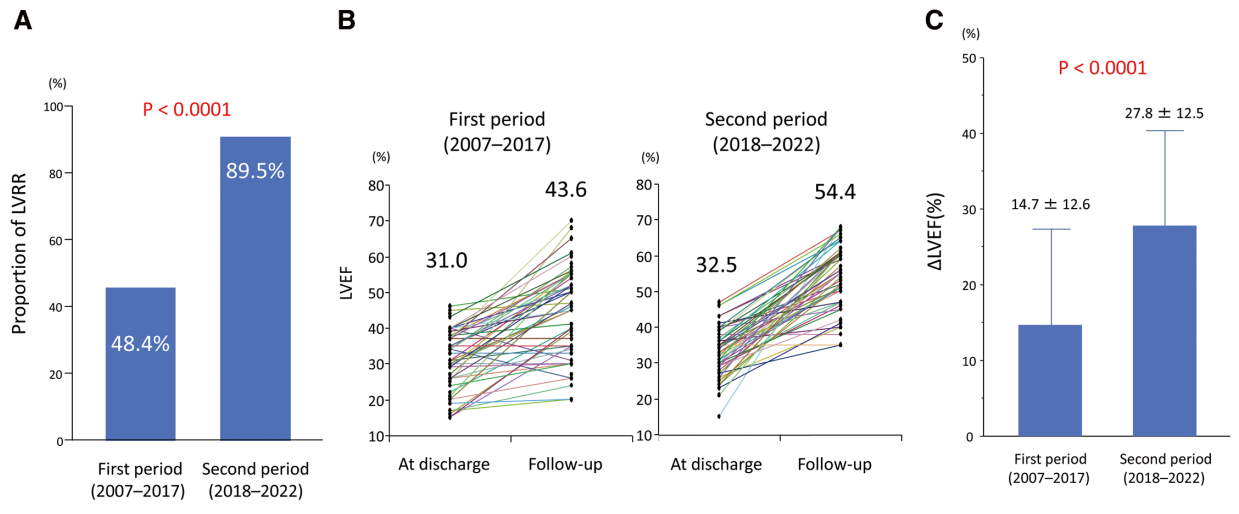

Figure 2. (**A**) Proportion of LVRR by year of diagnosis. LVRR was observed in 31 of 64 patients (48%) in the first period (2007–2017), and significantly increased to 51 of 57 patients (89%) in the second period (2018–2022). (**B**) Change in LVEF at discharge and follow-up. The mean maximum LVEF at follow-up was 43.6% for the first period and 54.4% for the second period. (**C**) Comparison of ΔLVEF between the first and second time periods. ΔLVEF was significantly higher in the second period than in the first. LVEF, left ventricular ejection fraction; LVRR, left ventricular reverse remodeling.

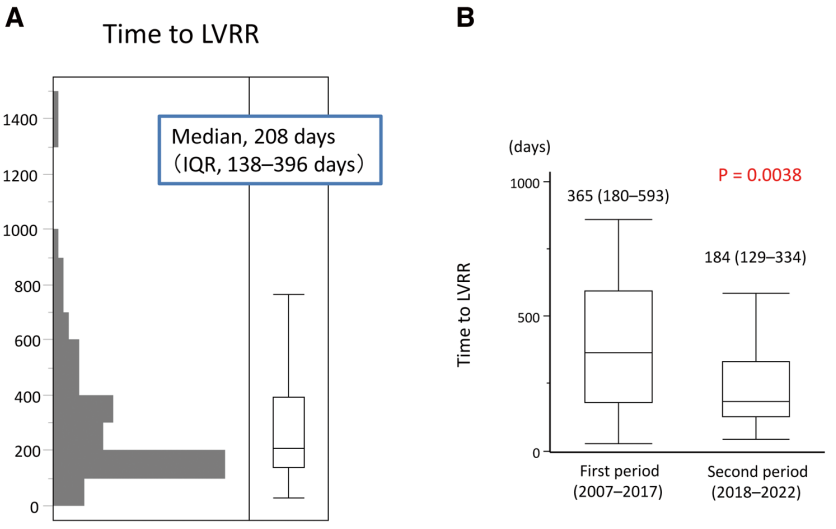

Figure 3. Histogram of the time to LVRR in 82 patients with LVRR. (**A**) The median time to LVRR was 208 days (interquartile range: 138–396 days). (**B**) Time to LVRR was significantly shorter in the second period than in the first, LVRR, left ventricular reverse remodeling.

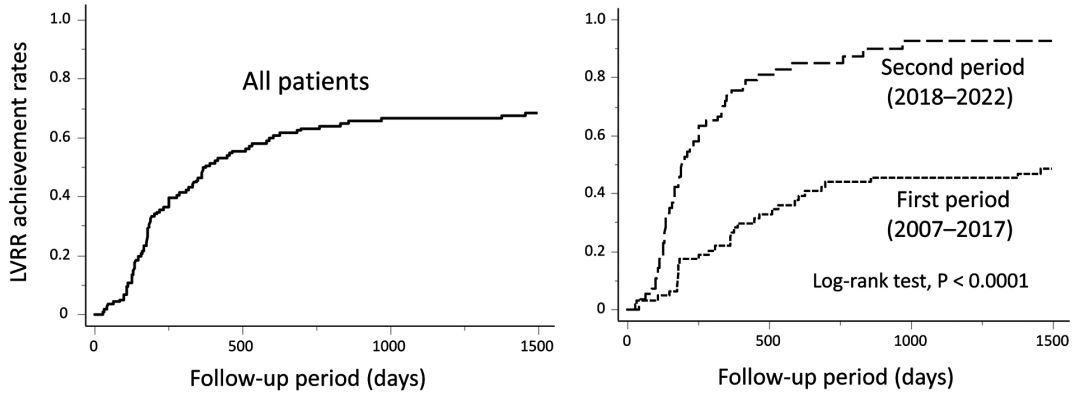

Figure 4. Kaplan-Meier analysis of LVRR achievement. In both the first and second time periods the rate of LVRR achievement reached a plateau in approximately 2 years, and LVRR was rarely observed thereafter. LVRR, left ventricular reverse remodeling.

The AUC for the BNP level at discharge was 0.74, and the cutoff value was 119 pg/mL (sensitivity, 0.74; specificity, 0.77) (**Figure 1B**).

Change in the LVRR Achievement Rate and Time to LVRR

Table 3 compares the patients' characteristics for the first and second time periods. There was no significant difference in age, sex, BMI, duration of hospitalization, presence of a family history of cardiomyopathy, hypertension, diabetes, AF, LVEF at diagnosis, LVDd at diagnosis, BNP at admission and discharge, or eGFR between the 2 time periods. The carvedilol equivalent dose increased significantly between the first and second time periods (14.1±6.5 vs. 18.9±8.8 mg/day). The use of ARNI (2% vs. 28%), MRA (44% vs. 65%), and SGLT2i (2% vs. 26%) significantly increased between the first and second time periods. The use of β-blockers (95% vs. 96%) and ACEi/ARB (90% vs. 98%) and the enalapril equivalent dose (5.0±3.0 mg/day vs. 5.5±3.0 mg/day) were not significantly different between time periods. Cardiac resynchronization therapy (CRT) was performed in 12 of 13 LBBB patients in the first time period, and in all 5 LBBB patients in the second time period. There was no statistically significant difference in the rate of CRT in LBBB patients between the first and second time periods.

Figure 2A compares the LVRR achievement rates between the first and second time periods. LVRR occurred in 31 of 64 patients (48%) in the first period and significantly increased to 51 of 57 patients (89%) in the second time period. The ΔLVEF is shown in **Figure 2B**,**C**. The mean maximum LVEF at follow-up was 43.6% in the first time period and 54.4% in the second. The ΔLVEF was significantly higher in the second period than in the first (27.8±12.5% vs. 14.7±12.6%, P<0.0001). A histogram of the time required to achieve LVRR in 82 patients with LVRR is shown in **Figure 3A**. The median time to LVRR in all patients was 208 days (IQR: 138–396 days). The time to LVRR was significantly shorter in the second time

period than in the first (184 [129–334] days vs. 365 [180–593] days, P=0.0038) (**Figure 3B**). Kaplan-Meier analysis of LVRR achievement showed that it reached a plateau in both the first and second time periods at approximately 2 years, and LVRR was rarely observed thereafter (**Figure 4**).

Relationship Between Genetic Variation and LVRR

Of the 27 patients who underwent genetic testing for cardiomyopathy-related genes, 10 had pathological variants, including 6 titin-truncating variants, 2 lamin A/C variants, and 2 others (a troponin T2 variant and a desmoplakin variant) (**Supplementary Figure 2A**, **Supplementary Table**). The relationship between genetic variation and the LVRR achievement rate is shown in **Supplementary Figure 2B**. LVRR was observed in 83% and 82% of patients with the titin-truncating variant and those without the variant, respectively. LVRR was not observed in the 2 patients with the lamin A/C variant.

Discussion

The main findings of the present study are as follows. (1) The proportion of patients with DCM who achieved LVRR was 68% and the rate showed an increase in recent years (48.4% vs. 89.5%). The median time to achieve LVRR was 208 days and has been shortening in recent years (365 days vs. 184 days). (2) Beta-blocker dose and BNP levels at discharge were independently associated with LVRR, with cutoff values of 15 mg/day of carvedilol and 119 pg/mL, respectively.

Improvement of LVRR Achievement Rate in DCM

LVRR is strongly associated with a good prognosis in cases of DCM.[6] In a previous study of DCM patients conducted between 1988 and 1997, LVRR was found in 37% of patients.[6] Previous studies using personal clinical records have reported that β-blockers and ACEi/ARBs are associated with LVRR in patients with DCM.[5,9] These drugs are currently used as standard therapies for HFrEF. According to a Japanese national registry of patients with DCM from 2003 to 2013, the prescription rates of ACEi/ARBs, β-blockers, and MRAs from 2011 to 2013 were 75.9%, 87.8%, and 39.7%, respectively. In particular, the prescription rate of β-blockers has increased in recent years.[18] The Japanese Circulation Society Guidelines on the Diagnosis and Treatment of Acute and Chronic Heart Failure were revised in 2018, and GDMT is now strongly recommended.[15] The treatment for DCM has also changed with the introduction of new drugs for treating HF, such as ARNI and SGLT2i. In the present study, the LVRR achievement rate after 2018 was 89%, and the prescription rates of ACEi/ARBs and β-blockers were 98% and 96%, respectively. The high prescription rates of these drugs may be responsible for the higher LVRR achievement rates in our study than has been previously reported. Although there are few reports on the use of ARNI to treat patients with DCM, they improve LVEF better than ACEi in HFrEF.[19] There are few reports on SGLT2i regarding LVRR, but there are a few reports of improved LVEF in HFrEF with this drug treatment.[20] In the present study, the prescription rates of ARNI and SGLT2i increased after 2018, which may have contributed to the improved LVRR achievement rate. The recently released 2023 Focused Update of the European Society of Cardiology guidelines recommends an intensive strategy of initiation and rapid up-titration of evidence-based treatment before discharge and during frequent and careful follow-up visits in the first 6 weeks after hospitalization for HF.[21]

Time to LVRR in DCM

LVEF is an important indicator of ICD treatment for HFrEF, and achievement of LVRR removes the need for device implantation. Current Japanese and international guidelines for treatment of cardiomyopathy recommend a 3-month drug treatment period to determine the ICD indication. However, few large studies have examined the time to achieve LVRR in DCM. Recently, the PROLONG study showed that of 156 patients with newly diagnosed LVEF <35% receiving a wearable cardioverter/defibrillator (WCD), 88 had a primary preventive ICD indication at 3-month follow-up, but only 58 showed a persistent primary preventive ICD indication at final follow-up (average 12 months).[11] In the present study, the median time to achieve LVRR was 208 days, and even after 2018, 184 days (i.e., approximately 6 months), suggesting that LVRR within 3 months is hardly achievable, although the time taken has been shortening in recent years. The decision for ICD therapy should be made when the LVEF is stable with no further improvement under optimal medical therapy, and extending the duration of WCD use may be a consideration in DCM. On the other hand, the results of this study suggest that the time to LVRR may continue to decrease with advances in DCM treatment.

Relationship Between Dose of Beta-Blocker and LVRR

In the present study, the dose of β-blockers was strongly associated with LVRR, with a carvedilol cutoff value of 15 mg/day. Furthermore, the results suggested that LVEF may improve in a dose-dependent manner. Beta-blockers induced high LVRR rates in patients with HFrEF.[22] However, whether the LVRR-inducing effect of β-blockers in treating HFrEF is dose-dependent remains controversial.[23–25] The MUCHA study, which examined the optimal dose of carvedilol for HFrEF in Japan, showed a dose-dependent trend toward greater improvement in LVEF, but there was no significant difference between the 5 mg/day and 20 mg/day groups.[24] The J-CHF study compared the efficacy of carvedilol at 3 different doses (2.5, 5, or 20 mg/day) in Japanese HFrEF patients and showed that LVEF and LVDd improved without a dose-response relationship.[25] However, a recent analysis of patients with DCM using the Japanese national database reported that β-blockers effectively prevented a decrease in LVEF in patients with improved DCM in a dose-dependent manner.[5] In both the MUCHA and J-CHF studies, approximately 30% of the HFrEF patients included in the study had an ischemic etiology, which may have affected the results because it is known to be more difficult to obtain LVRR with ischemic heart disease than with a non-ischemic etiology.[26] Beta-blockers may improve LVEF and prevent recurrent LV dysfunction in DCM in a dose-dependent manner, and should be administered at recommended doses whenever possible.

Relationship Between BNP Levels and LVRR

Previous studies examining LVRR-related factors in DCM showed that the BNP levels during follow-up, but not those at baseline, were associated with LVRR.[27,28] In the present study, the BNP levels at discharge were strongly associated with LVRR, with a cutoff value of 119 pg/mL;

however, BNP levels at admission were not associated with LVRR. BNP levels at discharge may reflect treatment response approximately 1 month after treatment initiation, because the median duration of hospitalization in this study was 23 days. Therefore, it is likely that the BNP levels at discharge were associated with LVRR in this study, as well as the BNP levels during follow-up in previous reports. A low pulmonary artery wedge pressure (PAWP) measured by right heart catheterization is an independent predictor of LVRR in patients with DCM.[29] Because BNP levels are strongly associated with PAWP, it seems reasonable that lower BNP levels would be associated with achieving LVRR. Whether BNP-guided treatment improves prognosis in the management of HF remains inconclusive, although a recent meta-analysis suggested a reduction in mortality and re-hospitalization rates for HF.[30–32] These results suggest that BNP-guided treatment may be effective in improving the prognosis of DCM.

Study Limitations

There are several to consider. First, this was a single-center observational study with a relatively small study population, which therefore requires caution when interpreting the results. Second, contrast-enhanced cardiac magnetic resonance imaging was not performed for all patients, and the association between late gadolinium enhancement and LVRR was not examined. Third, ARNI and SGLT2i, which are currently recommended for HFrEF, only became available in Japan after 2020; therefore, the prescription rates for these drugs were low in this study. Fourth, the survival and LVRR achievement rates of the patients excluded due to lack of follow-up echocardiography are unknown. Fifth, our hospital has focused on cardiac rehabilitation as well as medication in recent years, but the impact of this has not been investigated. Sixth, the proportion of patients with genetic variants among those who underwent genetic testing was lower than that reported in previous studies.

Conclusions

Recent advances in treatment may have both increased the proportion of patients with DCM who achieve LVRR and shortened the time to LVRR. Beta-blockers were associated with LVRR in a dose-dependent manner, and BNP levels at discharge after initial treatment were strongly associated with LVRR in DCM.

Disclosures

I.K. is a member of *Circulation Reports*' Editorial Team.

IRB Information

The Ethical Review Committee of the Yamagata University Faculty of Medicine approved this study (Approval No. 2019-78).

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Supplementary Files

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