Nationwide Temporal Trends in Clinical Characteristics and Treatment of Dilated Cardiomyopathy From 2003 to 2013 in Japan: A Report From Clinical Personal Records

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https://hdl.handle.net/2324/7363656

出版情報：Kyushu University, 2024, 博士（医学）, 課程博士
バージョン：

Circulation Journal
Circ J 2023; 87: 500–507
doi:10.1253/circj.CJ-22-0554

ORIGINAL ARTICLE
Cardiomyopathy

Nationwide Temporal Trends in Clinical Characteristics and Treatment of Dilated Cardiomyopathy From 2003 to 2013 in Japan

— A Report From Clinical Personal Records —

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Background: Little is known about nationwide temporal trends in the clinical characteristics and treatment of dilated cardiomyopathy (DCM) in Japan.

Methods and Results: We collected data regarding demographics, echocardiography, and treatment of DCM between 2003 to 2013 from Clinical Personal Records, a national registry organized by the Japanese Ministry of Health, Labour, and Welfare. Among the 40,794 DCM patients screened, 27,702 with left ventricular ejection fraction (LVEF) <50% and age ≥18 years were enrolled in this study and divided into 3 groups according to registration year: Group 1, 2003–2005 (10,006 patients); Group 2, 2006–2010 (11,252 patients); and Group 3, 2011–2013 (6,444 patients). Over time, there were decreases in age at registration (mean [±SD] 58.6±13.0 vs. 56.8±13.8 vs. 56.2±13.8 years; P<0.001) and LVEF (33.5±10.0% vs. 31.1±9.9% vs. 29.2± 9.7%; P<0.001), and an increase in patients with New York Heart Association Class III–IV (28.2% vs. 35.2% vs. 41.0%; P<0.001). The use of β-blockers (59.1% vs. 79.3% vs. 87.8%; P<0.001) and mineralocorticoid receptor antagonists (30.6% vs. 35.8% vs. 39.7%; P<0.001) increased over time. In multivariate analysis, male sex, systolic blood pressure, chronic kidney disease, hemoglobin, and registration year were positively associated, whereas age and LVEF were negatively associated, with β-blocker prescription.

Conclusions: Although the clinical characteristics of DCM changed, the implementation of optimal medical therapy for DCM increased from 2003 to 2013 in Japan.

Key Words: Beta-blocker; Dilated cardiomyopathy; Nationwide temporal trend; Optimal medical therapy; Registry

Dilated cardiomyopathy (DCM) is defined as left ventricular (LV) systolic dysfunction and dilation in the absence of coronary artery disease or abnormal loading conditions sufficient to cause global LV impairment,[1] which is a major cause of heart failure with reduced ejection fraction (HFrEF). In several heart failure (HF) registries, DCM accounts for approximately 15% of the etiology among admitted HF patients,[2–5] and is the primary cause of heart transplantation in Japan.[6]

The therapeutic strategy against DCM is based on optimal medical therapy (OMT) for HFrEF.[7] Although, recently, angiotensin receptor-neprilysin inhibitor (ARNI) and sodium-glucose cotransporter 2 (SGLT2) inhibitors have been recommended for HFrEF,[8] β-blockers, angiotensin-converting enzyme inhibitors (ACEi)/angiotensin II receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs) are standard drugs used in treatment. The underuse of OMT is related to poor morbidity and mortality in HFrEF.[9,10] In 2002, a Japanese national survey showed that the prescription rates of β-blockers and ACEi for DCM were 41% and 65%, respectively,[11,12] indicating that OMT for DCM was insufficient in Japan. Subsequent studies reported on the implementation of OMT in HF has been reported in Japan.[4,13] Regarding DCM, a previous study reported temporal trends in the clinical features of and implementation of OMT for DCM patients by analyzing databases of the Chronic Heart Failure Analysis and Registry in Tohoku Distinct-1 Study (CHART-1 study; 2000–2005) and CHART-2 study (2006–2015).[14] However, the number of DCM patients in these studies was relatively small (CHART-1: 306 patients; CHART-2: 710 patients). Furthermore, they are regional

Received September 5, 2022; revised manuscript received January 18, 2023; accepted January 23, 2023; J-STAGE Advance Publication released online February 16, 2023 Time for primary review: 17 days
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ISSN-1346-9843

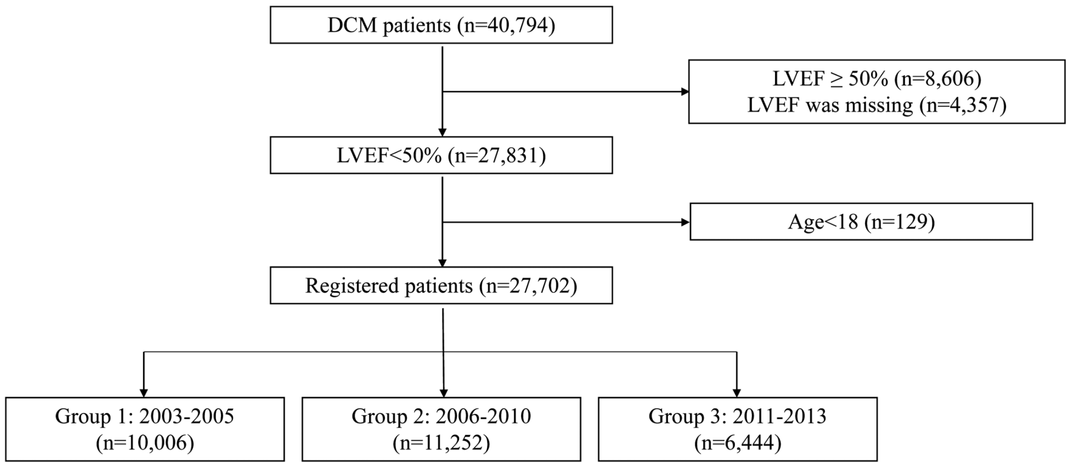

Figure 1. Patient selection. DCM, dilated cardiomyopathy; LVEF, left ventricular ejection fraction.

cohort studies of HF. To date, little is known about temporal trends in the clinical characteristics and treatment of DCM on a national scale in Japan.

Clinical Personal Records is a nationwide administrative database of public expenditure for refractory disease of the Japanese Ministry of Health, Labour, and Welfare that registers and certifies intractable diseases, including cardiomyopathy, throughout Japan. This database started registering information for DCM in 2003. In previous studies, we have used the Clinical Personal Records to report on the clinical features of DCM patients and routine practices, as well as the effectiveness of β-blockers and ACEi/ARB on LV reverse remodeling in DCM.[15–18] This database is the largest and most reliable for investigations into clinical information regarding DCM in Japan. The aim of the present study was to describe temporal trends in the clinical characteristics and medical treatment of DCM in Japan using the nationwide Clinical Personal Records database.

Methods

Clinical Personal Records

The following information was obtained from the Clinical Personal Record database: (1) demographic data (age, sex, and New York Heart Association [NYHA] functional class); (2) vital signs; (3) laboratory data; (4) electrocardiographic data; (5) echocardiographic data; and (6) medication use.[15] The Clinical Personal Record database does not contain information about clinical outcomes, such as hospitalization and death. All personal clinical records were registered after being reviewed by certified cardiologists. We examined the baseline data registered for each patient.

Diagnostic Criteria

DCM was diagnosed on the basis of LV dilatation and reduced LV ejection fraction (LVEF) in the absence of any specific cardiac or systemic diseases, such as hypertensive heart disease, valvular heart disease, congenital heart disease, coronary artery disease, alcoholic cardiomyopathy, cardiomyopathy caused by toxins/medications, amyloidosis, sarcoidosis, connective tissue disease, dystrophy, or metabolic diseases such as Pompe disease or Fabry disease.

Study Patients

From the Clinical Personal Records database, DCM patients with LVEF <50% and age ≥18 years were enrolled in this study. In Japan, HF guidelines were published in 2005 and 2010. To reveal the treatment landscape before and after the publication of these guidelines, eligible patients were divided into 3 groups according to registration year: Group 1, 2003–2005; Group 2, 2006–2010; and Group 3, 2011–2013. The features and management of each of these groups were described.

Dose Equivalents for Carvedilol and Bisoprolol

The dose equivalents for carvedilol and bisoprolol were derived from the Japanese Circulation Society Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure.[19] In short, 5 mg bisoprolol was determined to be equivalent to 20 mg carvedilol.

Statistical Analysis

Patient characteristics, including age, sex, NYHA functional class, vital signs, comorbidities, laboratory data, electrocardiographic findings, echocardiographic findings, and medications were compared among groups using the χ^2 test for categorical variables and analysis of variance for continuous variables; data are presented as the mean ± SD or the median with interquartile range (IQR). Univariate and multivariate logistic models were used to assess correlations between the prescription of β-blockers or MRAs and other variables. All tests were 2-tailed and $P<0.05$ was considered statistically significant. The analyses were conducted using SAS®9.4 (SAS Institute, Cary, NC, USA).

Ethics Statement

This study was performed based on the principles of the Declaration of Helsinki. The original study protocol was approved by the Institutional Review Board (IRB) at Kyushu University (No. 29-48). The authors had full access to the data and take full responsibility for their integrity. Because this study investigated a nationwide administra-

Table 1. Patient Characteristics

	Group 1 (n=10,006)	Group 2 (n=11,252)	Group 3 (n=6,444)	P value	No. missing values
Demographics					
Age at registration (years)	58.6±13.0	56.8±13.8	56.2±13.8	<0.001	0
Age at diagnosis (years)	53.3±13.2	53.6±13.9	53.9±14.0	0.02	0
Male sex	7,529 (75.2)	8,432 (74.9)	4,893 (75.9)	0.34	0
NYHA Class III–IV	2,697 (28.2)	3,783 (35.2)	2,540 (41.0)	<0.001	1,201
Family history					
Cardiomyopathy	87 (3.2)	238 (3.4)	197 (3.8)	0.02	12,907
Sudden cardiac death	87 (3.2)	165 (2.4)	120 (2.3)	0.03	7,284
Vital signs					
SBP (mmHg)	119.5±19.8	119.5±22.2	120.6±23.3	0.003	1,659
DBP (mmHg)	72.7±14.2	74.1±16.6	75.9±17.8	<0.001	1,719
Heart rate (beats/min)	76.5±18.1	82.0±21.6	85.4±22.7	<0.001	3,230
Comorbidities					
Hypertension	563 (5.6)	1,168 (10.4)	913 (14.2)	<0.001	0
Diabetes	301 (3.0)	296 (2.6)	284 (4.4)	<0.001	0
CKD Stage III–V	4,290 (42.9)	4,545 (40.4)	2,627 (40.8)	<0.001	0
Laboratory data					
Hemoglobin (g/dL)	13.9±1.9	14.0±2.0	14.1±2.0	<0.001	1,424
Creatinine (md/dL)	0.90 [0.74–1.10]	0.9 [0.74–1.10]	0.9 [0.76–1.10]	0.008	984
Uric acid (mg/dL)	6.7±2.0	6.9±2.1	7.1±2.2	<0.001	5,170
Potassium (mEq/L)	4.22±0.46	4.25±0.47	4.23±0.48	0.003	1,770
BNP (pg/mL)	151.0 [48.5–440.0]	250.9 [73.5–691.3]	329.4 [97.0–835.1]	<0.001	6,506
Electrocardiographic findings					
Atrial fibrillation	2,372 (23.7)	2,575 (22.9)	1,420 (22.0)	0.04	0
Pacemaker	266 (2.7)	334 (3.0)	178 (2.8)	0.38	0
Left bundle branch block	614 (6.1)	967 (8.6)	649 (10.1)	<0.001	0
Echocardiographic findings					
LVEF (%)	33.5±10.0	31.1±9.9	29.2±9.7	<0.001	0
LVDd (mm)	62.3±9.1	62.8±8.8	63.0±8.5	<0.001	619
LVDs (mm)	52.1±9.9	53.2±9.6	54.0±9.3	<0.001	1,138
MR III–IV	1,112 (14.3)	1,616 (17.7)	956 (18.0)	<0.001	5,494

Unless specified otherwise, data are shown as n (%), mean±SD, or the median [interquartile range]. BNP, B-type natriuretic peptide; CKD, chronic kidney disease; DBP, diastolic blood pressure; LVDd, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; SBP, systolic blood pressure.

tive database (unconnectable anonymized data), we could not obtain informed consent from each patient. As a result, we announced our research on our homepage for a specific amount of time instead of obtaining informed consent.

Results

Patient Characteristics

In the Clinical Personal Records database data were available for 40,794 consecutive patients with DCM registered between 2003 and 2013. After screening, 27,831 patients with LVEF <50% were identified; of these, 129 were under 18 years of age and were excluded. Thus, 27,702 patients were included in the present analysis; of these, 10,006, 11,252, and 6,444 were classified in Group 1, Group 2, and Group 3, respectively (**Figure 1**). The clinical characteristics of the DCM patients in each group are presented in **Table 1**. Over time (i.e., in Group 1 vs. Group 2, vs. Group 3), there were decreases in both age at registration (58.6±13.0 vs. 56.8±13.8 vs. 56.2±13.8 years; P<0.001) and age at diagnosis (53.3±13.2 vs. 53.6±13.9 vs. 53.9± 14.0 years; P=0.02), but an increase in the percentage of patients with NYHA Class III–IV (28.2% vs. 35.2% vs. 41.0%; P<0.001). There was an increase in a family history of cardiomyopathy over time (3.2% vs. 3.4% vs. 3.8%; P=0.02), but a decrease in sudden death (3.2% vs. 2.4% vs. 2.3%; P=0.03). In term of comorbidities, the prevalence of both hypertension (5.6% vs. 10.4% vs. 14.2%, P<0.001) and diabetes (3.0% vs. 2.6% vs. 4.4%, P<0.001) increased over time; the prevalence of chronic kidney disease (CKD) Stage III–V decreased from Group 1 to Groups 2 and 3 (42.9% vs. 40.4% vs. 40.8%; P<0.001). In laboratory data, B-type natriuretic peptide (BNP) concentrations increased over time (151.0 vs. 250.9 vs. 329.4pg/mL; P<0.001), and hemoglobin, creatinine, and potassium increased slightly. The echocardiographic analysis showed that LVEF decreased over time (33.5±10.0% vs. 31.1±9.9% vs. 29.2± 9.7%; P<0.001), but LV diastolic diameter (LVDd; 62.3±9.1 vs. 62.8±8.8 vs. 63.0±8.5mm; P<0.001) and LV systolic diameter (52.1±9.9 vs. 53.2±9.6 vs. 54.0±9.3mm, P<0.001) increased gradually. In addition to the increases in the severity of DCM as demonstrated above, left bundle branch block increased over time (6.1% vs. 8.6% vs. 10.1%; P<0.001).

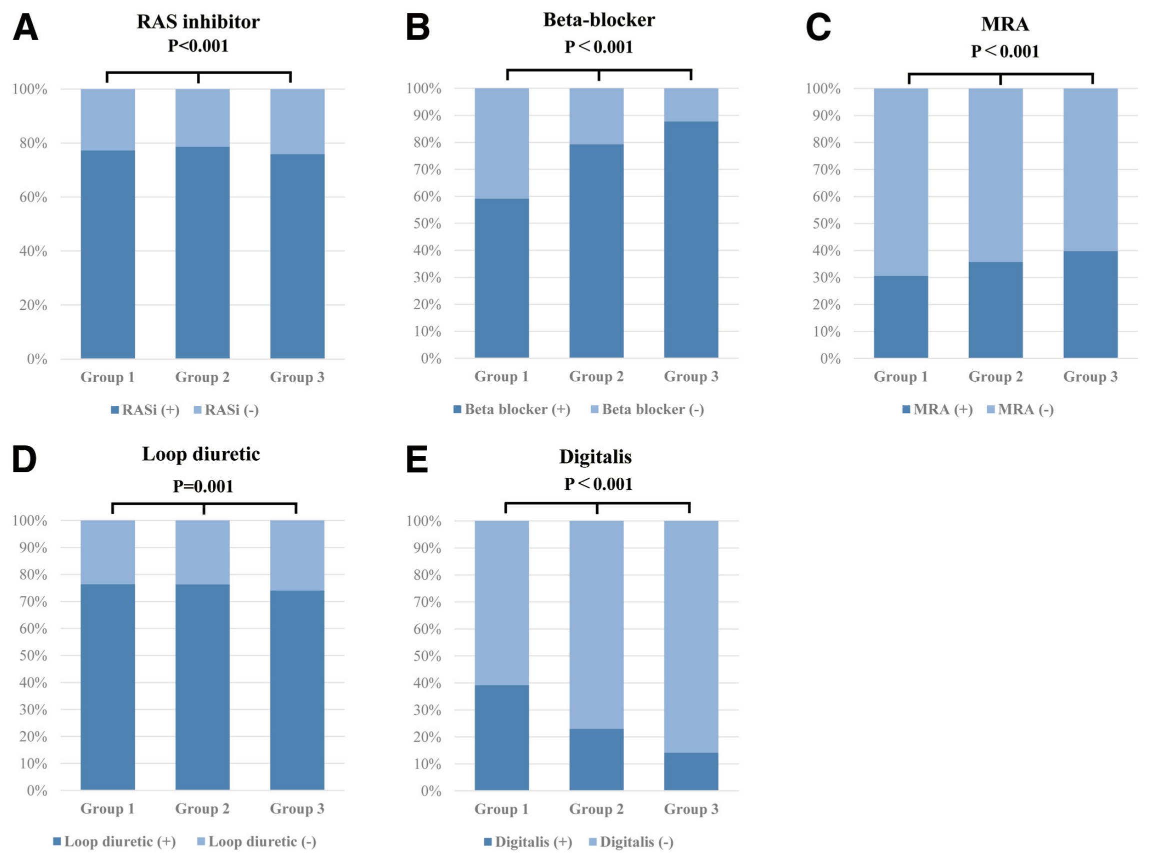

Figure 2. Temporal trends in medical treatment in patients with dilated cardiomyopathy. Patients were divided into 3 groups according to registration year: Group 1, 2003–2005; Group 2, 2006–2010; and Group 3, 2011–2013. MRA, mineralocorticoid receptor antagonist; RAS, renin-angiotensin system; RASi, renin-angiotensin system inhibitor.

Temporal Trends in Medical Treatment in DCM

The prescription rate of ACEi/ARB was slightly decreased in Group 3 compared with Groups 1 and 2 (75.9% vs. 77.3% and 78.6%, respectively; P<0.001; **Figure 2A**). The prescription rates of β-blockers (carvedilol or bisoprolol; 59.1% vs. 79.3% vs. 87.8%; P<0.001; **Figure 2B**) and MRAs (30.6% vs. 35.8% vs. 39.7%; P<0.001; **Figure 2C**) increased over time from Group 1 to Groups 2 and 3. Conversely, the number of patients receiving loop diuretics (76.4% vs. 76.3% vs. 74.0%, P=0.001; **Figure 2D**) and digitalis (39.2% vs. 23.0% vs. 14.2%, P<0.001; **Figure 2E**) decreased over time.

Doses of β-Blockers in DCM Patients

Figure 3 shows the distribution of β-blocker doses standardized in carvedilol units in each group. The number of people prescribed ≤10 mg carvedilol increased from Group 1 to Groups 2 and 3 (42.1% vs. 61.4% vs. 66.8%; P<0.001). In addition, more patients in Group 3 than in Groups 1 and 2 had prescriptions for carvedilol doses >10 mg (14.7% vs. 12.3% and 12.6%, respectively; P<0.001).

Factors Associated With the Prescription of β-Blockers

To elucidate factors associated with the prescription of β-blockers in DCM patients, we conducted univariate and multivariate analyses. BNP was excluded from these anal-

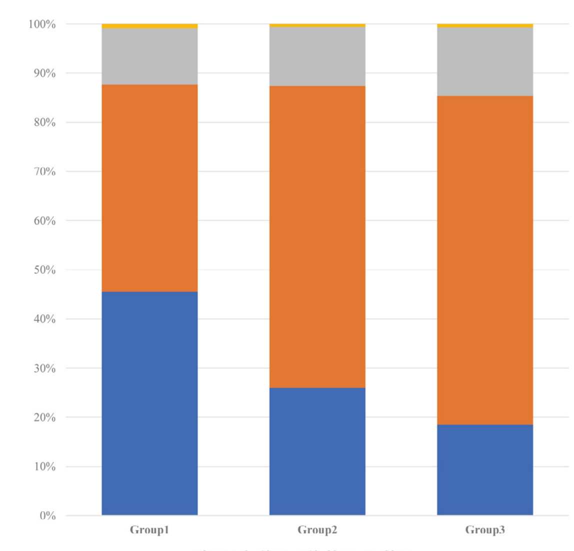

Figure 3. Prescribed doses of β-blockers in patients with dilated cardiomyopathy. The dose of β-blockers was standardized as carvedilol units. Patients were divided into 3 groups according to registration year: Group 1, 2003–2005; Group 2, 2006–2010; and Group 3, 2011–2013.

Table 2. Univariate and Multivariate Analysis for β-Blocker Prescription

Variable	Univariate analysis		Multivariate analysis	
	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value
Age at registration (years)	0.98 (0.98–0.98)	<0.001	0.99 (0.987–0.996)	<0.001
Male sex	0.92 (0.87–0.98)	0.010	1.16 (1.015–1.315)	0.03
NYHA class III–IV	1.11 (1.04–1.17)	<0.001	0.92 (0.819–1.024)	0.12
SBP (per 10-mmHg increment)	0.99 (0.98–1.01)	0.42	1.04 (1.017–1.070)	0.001
Heart rate (per 10-beats/min increment)	1.08 (1.06–1.10)	<0.001	1.01 (0.987–1.043)	0.31
Hypertension	0.61 (0.55–0.67)	<0.001	1.00 (0.868–1.145)	0.97
CKD Stage III–V	1.18 (1.12–1.25)	<0.001	1.11 (1.000–1.240)	0.049
Hemoglobin	1.07 (1.05–1.08)	<0.001	1.06 (1.024–1.087)	<0.001
Potassium	1.07 (1.00–1.14)	0.045	1.06 (0.941–1.185)	0.36
Atrial fibrillation	1.27 (1.19–1.35)	<0.001	1.12 (0.995–1.261)	0.06
Pacing	0.92 (0.78–1.08)	0.3		
LVEF	0.98 (0.98–0.98)	<0.001	0.99 (0.986–0.998)	0.01
LVDd	1.01 (1.01–1.01)	<0.001	1.00 (0.992–1.006)	0.76
MR III–IV	0.95 (0.88–1.04)	0.25		
Registration year	1.24 (1.23–1.25)	<0.001	1.15 (1.128–1.166)	<0.001

CI, confidence interval. Other abbreviations as in Table 1.

Table 3. Univariate and Multivariate Analysis for MRA Prescription

Variable	Univariate analysis		Multivariate analysis	
	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value
Age at registration (years)	0.99 (0.99–0.99)	<0.001	1.00 (0.993–0.999)	0.02
Male sex	1.13 (1.07–1.20)	<0.001	1.20 (1.075–1.340)	0.001
NYHA Class III–IV	1.51 (1.44–1.60)	<0.001	1.30 (1.183–1.433)	<0.001
SBP (per 10-mmHg increment)	0.91 (0.90–0.92)	<0.001	0.94 (0.924–0.965)	<0.001
Heart rate (per 10-beats/min increment)	1.09 (1.07–1.10)	<0.001	1.02 (1.000–1.049)	0.046
Hypertension	0.83 (0.77–0.90)	<0.001	0.91 (0.809–1.029)	0.13
CKD Stage III–V	0.98 (0.93–1.03)	0.41		
Hemoglobin	1.02 (1.01–1.03)	0.003	1.04 (1.010–1.064)	0.006
Potassium	1.06 (1.00–1.13)	0.049	0.89 (0.805–0.980)	0.02
Atrial fibrillation	1.06 (1.00–1.12)	0.053		
Pacing	0.84 (0.72–0.97)	0.018	0.98 (0.681–1.408)	0.91
LVEF	0.97 (0.97–0.98)	<0.001	0.98 (0.978–0.988)	<0.001
LVDd	1.02 (1.02–1.02)	<0.001	1.01 (1.004–1.017)	<0.001
MR III–IV	0.80 (0.74–0.86)	<0.001	0.94 (0.838–1.042)	0.23
Registration year	1.24 (1.23–1.25)	<0.001	1.03 (1.014–1.044)	<0.001

Abbreviations as in Tables 1,2.

yses because of many missing values. CKD was used in these analyses in place of creatinine because of the confounding relationship between CKD and creatinine. Furthermore, diabetes was excluded because it obviously seems to be clinically less relevant for β-blocker prescriptions and its prevalence rate was low. The univariate analysis demonstrated that age, male sex, NYHA functional class, heart rate, hypertension, CKD, hemoglobin, potassium, atrial fibrillation, LVEF, LVDd, and registration year were associated with the prescription of β-blockers (**Table 2**). In addition to these factors, systolic blood pressure (SBP) was included in the multivariate model because, in general, blood pressure is intimately involved in β-blocker administration. The multivariate analysis revealed that male sex, SBP, CKD, hemoglobin, and registration year were positively associated, but age and LVEF were negatively associated, with the prescription of β-blockers (**Table 2**). These findings show that, despite changes in the clinical features of DCM patients, β-blocker prescriptions increased over time.

Factors Associated With MRA Prescriptions

We also determined factors associated with the prescription of MRAs in DCM patients. The univariate analysis included the same factors as used in the analysis of β-blocker prescriptions. The univariate analysis showed that age, male sex, NYHA functional class, SBP, heart rate, hypertension, hemoglobin, potassium, pacing, LVEF, LVDd, mitral regurgitation, and registration year were associated with the prescription of MRAs (**Table 3**). These factors were included in the multivariate analysis, which revealed that NYHA functional class, heart rate, hemoglobin, LVDd, and registration year were positively associated, but age, SBP, potassium, and LVEF were negatively associated, with the prescription of MRAs (**Table 3**). These results indicate that, as with β-blocker prescriptions, MRA prescriptions increased over time.

Discussion

The present study demonstrated that the severity of the disease state (e.g., NYHA functional class, BNP concentrations, and LV dysfunction) and the prevalence of comorbidities (e.g., hypertension and diabetes) increased in DCM patients from 2003 to 2013 in Japan. The prescription rates of β-blockers and MRAs for DCM patients also increased. Conversely, prescriptions for loop diuretics and digitalis decreased. Although the clinical features of DCM patients changed over time, OMT, such as treatment with β-blockers and MRAs, was implemented for DCM patients in Japan.

The present study showed the nationwide temporal trends in the clinical characteristics of DCM patients in Japan. Whereas age at diagnosis increased over time, age at registration decreased. These trends may reflect the aging of DCM patients and their early registration after diagnosis. The number of patients with NYHA Class III–IV and BNP concentrations increased and LVEF decreased, demonstrating worsening severity of DCM in patients at registration. Conversely, the CHART studies reported conflicting finding, namely decreases in NYHA Class III–IV and increases in LVEF in DCM patients.[14] Importantly, the present study enrolled DCM patients with LVEF <50%, whereas the CHART studies are considered to include patients with HF with preserved ejection fraction or HF with improved ejection fraction. The discrepancy in clinical characteristics between the CHART studies and the present study may be due to the difference in patient selection. In addition, our findings suggest that severe DCM cases may have been detected in Japan. Another important finding of the present study was an increase in comorbidities, such as hypertension and diabetes, over time. This trend is consistent with the CHART studies, indicating westernization of the clinical background of DCM patients in Japan. However, compared with CHART studies, the prevalence rates of these comorbidities were lower in the present study. We hypothesize that the registration of younger patients in the present study accounts for this difference. The number of HF patients with CKD increases steadily with age.[20] However, the number of patients with CKD Stage III–V was decreased among the DCM patients in the present study. This is also thought to be associated with younger age registration in the present study. In the laboratory data, there were increases in hemoglobin, creatinine, and potassium over time, but these changes seem clinically non-significant.

The underuse of β-blockers, ACEi/ARBs, and MRAs results in poor morbidity and mortality in HFrEF.[9,10] We have recently shown that the use of ACEi/ARBs is related to reverse LV remodeling in DCM patients.[17,18] In addition, the use of β-blockers was associated with the prevention of LV dysfunction in reversed DCM.[16] LV reverse remodeling is a surrogate endpoint in HF clinical trials.[21] Previous national surveys in Japan in 2002 revealed that the prescription rates of β-blockers and ACEi for DCM were 41% and 65%, respectively,[11,12] indicating insufficient OMT for DCM patients. However, in the present study, the prescription rate of β-blockers was 59.1% in 2003–2005, which increased to 87.8% in 2011–2013 (**Figure 2B**). As with β-blockers, the use of MRAs increased over time from 30.6% to 39.7% (**Figure 2C**). Although the prescription of ACEi/ARBs was slightly reduced in Group 3 (**Figure 2A**), this difference does not seem to be clinically significant. These data are consistent with results from the CHART studies.[14] In 2003–2005, a sizable percentage of DCM patients (77.3%) were already prescribed ACEi/ARBs. This may explain the nearly constant prescription rate of ACEi/ARBs over time.

We investigated factors related to the prescription of β-blockers (**Table 2**). Multivariate analysis demonstrated that age and LVEF were negatively associated, whereas SBP was positively associated, with the prescription of β-blockers. These findings seem to be explained by clinical practice, in that β-blockers are easy to prescribe to younger patients with higher SBP, to prevent its side effects, including hypotension, and are likely to be prescribed to patients with lower LVEF in order to achieve reverse remodeling. Sex differences in OMT are known to depend on study cohorts.[22,23] According to our findings, male DCM patients are more likely than female DCM patients to receive a prescription for a β-blocker. Hemoglobin was positively related to β-blocker prescriptions in the present study. Several previous studies reported that anemic patients with HF receive β-blockers less frequently.[24,25] Furthermore, anemia is associated with a blunted response to carvedilol.[26] The relationship between hemoglobin and β-blocker prescriptions is interesting. However, further investigations are needed to elucidate it. CKD is the most crucial prognostic factor in HF patients.[19] Beta-blockers are beneficial for HF patients with advanced renal dysfunction.[27,28] Whereas the prevalence of CKD Stage III–V decreased over time (**Table 1**), CKD was positively associated with β-blocker prescriptions (**Table 2**). Aggressive β-blocker prescription for CKD may contribute to better prognosis in DCM patients, as shown in the CHART-2 study.[14]

Factors related to the prescription of MRAs were also analyzed (**Table 3**). Multivariate analysis revealed that age, male sex, hemoglobin, and LVEF were associated with MRA prescriptions, as for β-blockers. NYHA functional class and LVDd were also related to MRA prescriptions. This may be an aggressive prescription to improve the condition of patients with severe DCM. Potassium was negatively associated with MRA prescriptions. This may be due to clinical practice, whereby MRA use is avoided for hyperkalemia. Curiously, heart rate was positively associated with MRA prescriptions. However, the causal relationship between these 2 is unclear because the present study was a cross-sectional study.

Importantly, registration year was positively associated with the prescription of β-blockers and MRAs (**Tables 2**,**3**). These results show that, although the clinical characteristics of DCM changed over time, prescriptions for β-blockers and MRAs increased. Clinical evidence for the use of β-blockers and MRAs was established in the 1990s.[29,30] After the 2000s, the HF guidelines recommended OMT, including β-blockers and MRAs, for HFrEF.[31,32] Our results imply that the dissemination of the HF and cardiomyopathy guidelines may lead to implementation of OMT for DCM.

The present study presented the dose of β-blockers prescribed to DCM patients in Japan standardized in carvedilol units. The number of people with a carvedilol-equivalent dose of ≤10 mg increased over time (**Figure 3**). Even though the prescription rate of β-blockers was increased, heart rate also increased over time (**Table 1**). This may be due to the increased severity of HF at registration, as discussed above. Importantly, the multivariate analysis showed that heart rate was not associated with the prescription of β-blockers, indicating that differences in heart rate did not affect the temporal trend in β-blocker prescriptions.

Most recent HF guidelines recommend ARNI and SGLT2 inhibitors for HFrEF patients,[8,33,34] and both drugs are effective for DCM patients.[35,36] To enhance OMT implementation for DCM, further research on the latest treatment information, including ARNI and SGLT2 inhibitors, is required.

Study Limitations

There are several potential limitations to be acknowledged in the present study. First, the database used does not include information regarding genetic testing, non-pharmacological therapy, and outcomes, including hospitalization and death. Second, the reason why some patients did not receive OMT, such as a patient's request, bradycardia, hypotension, and comorbidities, including asthma, chronic obstructive pulmonary disease, and CKD, could not be determined. Third, the Clinical Personal Record is an administrative database. The data were collected at various time points (e.g., for inpatients and outpatients). However, it is difficult to identify these time points in this study. Finally, the present study is a cross-sectional study. The causal relationship between drug prescription and related factors is unclear. Despite the limitations described above, we analyzed the largest database that included more than 27,000 DCM patients, supporting the conclusion drawn in the present study.

Conclusions

By analyzing a nationwide database of more than 27,000 patients with DCM, this study reveals that, whereas clinical characteristics in DCM patients changed, OMT (e.g., β-blocker and MRA prescriptions) for DCM increased from 2003 to 2013 in Japan. In a new era of HF treatment, including ARNI and SGLT2 inhibitors, further implementation of OMT for DCM is needed.

Acknowledgments

The authors thank cardiologists in the survey institutions for allowing us to obtain the data.

Sources of Funding

This work was supported by Health Sciences Research Grants from the Japanese Ministry of Health, Labour, and Welfare (Comprehensive Research on Cardiovascular Diseases) to H.T. (20FC1051).

Disclosures

H.T. reports personal fees from MSD, Astellas, Pfizer, Bristol-Myers Squibb, Otsuka Pharmaceutical, Daiichi-Sankyo, Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim, Takeda Pharmaceutical, Bayer Yakuhin, Novartis Pharma, Kowa Pharmaceutical, Teijin Pharma, Medical Review Co., and the *Japanese Journal of Clinical Medicine*; non-financial support from Actelion Pharmaceuticals, Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim, Daiichi-Sankyo, IQVIA Services Japan, and Omron Healthcare Co.; and grants from Astellas, Novartis Pharma, Daiichi-Sankyo, Takeda Pharmaceutical, Mitsubishi Tanabe Pharma, Teijin Pharma, and MSD, outside the submitted work. H.T. and T.I. are members of *Circulation Journal*'s Editorial Team. The remaining authors declare no conflicts of interest associated with this manuscript.

IRB Information

The original study protocol was approved by the Institutional Review Board at Kyushu University (No. 29-48).

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