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Research paper

Beta-blockers are associated with reverse remodeling in patients with dilated cardiomyopathy and mid-range ejection fraction

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ABSTRACT

Background: Beta-blockers have been shown to induce left ventricular reverse remodeling (LVRR) in heart failure with reduced ejection fraction. This study aimed to determine whether beta-blockers could induce LVRR in patients with heart failure with mid-range ejection fraction (HFmrEF).

Methods: We analyzed the national database from clinical personal records of dilated cardiomyopathy (DCM) maintained by Japanese Ministry of Health, Labour and Welfare, between 2003 and 2014. Patients with left ventricular ejection fraction (LVEF) of ≥40% and < 50% were included. Patients who did not have echocardiography at 2 years of follow-up were excluded. Eligible patients were divided into two groups according to the use of beta-blockers. Patient characteristics of two groups were adjusted by propensity score matching. The primary outcome was LVRR at 2 years of follow-up, defined as an improvement in LVEF ≥10%.

Results: Out of 3064 patients, propensity score matching yielded 602 pairs. The mean age was 59.3 years and 896 patients (74.4%) were male. The primary outcome was observed more frequently in beta-blocker group (24.3% vs. 17.8%; Odds ratio [OR], 1.48; 95% confidence interval [CI], 1.12–1.96; $P = 0.006$). Subgroup analysis demonstrated that patients with heart rate ≥ 75 bpm (≥ 75 bpm; OR, 2.61; 95% CI, 1.66–4.11: < 75 bpm; OR, 1.03; 95% CI, 0.72–1.48; P for interaction = 0.002) and atrial fibrillation (AF) (AF; OR, 2.30; 95% CI, 1.37–3.86: No AF; OR 1.23; 95% CI, 0.88–1.72; P for interaction = 0.046) were benefited by beta-blockers.

Conclusions: Beta-blockers could induce LVRR in patients with DCM and HFmrEF.

1. Introduction

Heart Failure (HF) with a left ventricular ejection fraction (LVEF) between 40 and 49% was first proposed in 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines as an intermediate group. [1] The 2016 European Society of Cardiology (ESC) HF guidelines specified this distinct group as HF with mid-range ejection fraction (HFmrEF) to propose more research on this clinical entity. [2] Recently, the 2021 ESC HF guideline has changed the term 'heart failure with mid-range ejection fraction' to 'heart failure with mildly reduced ejection fraction'. [3] HFmrEF is known to share common clinical features with other HF phenotypes. HFmrEF has a high prevalence of ischemic etiology, as in HF with reduced ejection fraction (HFrEF) (LVEF <40%), or hypertension and diabetes, as in HF with preserved ejection fraction (HFpEF) (LVEF ≥50%). [4] The mortality and rehospitalization in HFmrEF were comparable with HFpEF and HFrEF. [5–7] Recently, several studies have demonstrated that LVEF variations is common in HFmrEF. Transition from HFmrEF toward HFpEF and HFrEF has been reported in 25–44% and in 16–33% of patients, respectively. [8–10] Importantly, HFmrEF

Abbreviations: HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HF, heart failure; LVEF, left ventricular ejection fraction; LVRR, left ventricular reverse remodeling; DCM, dilated cardiomyopathy; OR, odds ratio; CI, confidence interval.

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patients moving toward HFpEF are characterized by lower mortality and better functional capacity compared with those with HFrEF or HFmrEF who does not transit. [11–13] Thus, LV reverse remodeling, defined as an increase in LVEF, is thought to be a cornerstone of prognosis in HFmrEF. [4]

Two retrospective studies and a recent meta-analysis demonstrated that beta-blockers reduced cardiovascular mortality among patients with HFmrEF. [14–16] Beta-blockers also improved LV systolic function in HFmrEF. [14] The 2019 ESC clinical practice update on HF states that beta-blockers may be considered for ambulatory patients with symptomatic HFmrEF in sinus rhythm. [17] However, in most previous studies, the majority of HFmrEF patients had ischemic etiology. Although dilated cardiomyopathy (DCM) is not a negligible cause of HFmrEF, [18] limited data are available on characteristics and therapeutic responsiveness in DCM patients with HFmrEF.

The clinical personal record is a nationwide administrative database of public expenditure for refractory disease maintained by Japanese Ministry of Health, Labour and Welfare to register and certificate intractable diseases, including cardiomyopathies, throughout Japan. This database is useful to investigate clinical features and routine practice in DCM patients in Japan. [19] The aim of this study was to determine whether beta-blockers could induce LVRR in patients with DCM and HFmrEF by using the clinical personal record.

2. Methods

2.1. Clinical personal record

Clinical personal record of DCM has been established as a national database of public expenditure for refractory disease by Japanese Ministry of Health, Labour and Welfare. This record prospectively and annually collected the following data; (1) demographic data (age, gender, duration of HF, and NYHA functional class); (2) vital signs; (3) comorbidities; (4) electrocardiographic data; (5) echocardiographic data; (6) laboratory data; and (7) medication use. DCM was diagnosed on a dilated left ventricle and reduced 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 disease such as Pompe disease or Fabry disease. All clinical personal records were registered after review by certificated cardiologists. The present study employed this nationwide database from 2003 to 2014.

2.2. Patient selection

From the database of clinical personal records of DCM, those with LVEF of 40–50% and older than 18 years were enrolled in this study. Screened patients were excluded from enrollment if they received left ventricular assist device (LVAD) or heart transplantation during the follow-up period or they were not assessed with echocardiography at 2 years of follow-up. Patients prescribed with carvedilol or bisoprolol were assigned to beta-blocker group and those not prescribed were no beta-blocker group. All patients had any prior symptoms or signs of HF, including dyspnea, palpitation, chest pain, edema, and hepatomegaly.

2.3. Outcomes

Primary outcome of this study was the LVRR at 2 years of follow-up, defined as an increase in LVEF $\geq$10%. Secondary outcomes were a decrease in left ventricular diastolic diameter (LVDd) $\geq$ 10% and a decrease in LV systolic diameter (LVDs) $\geq$ 10%. Factors associated with an increase in LVEF, including changes in systolic blood pressure, diastolic blood pressure, heart rate, prescription rates of angiotensin-converting-enzyme inhibitors (ACEi), angiotensin-receptor-blockers (ARB), digitalis, and biventricular pacing at 2 years of follow-up, were also assessed. We also assessed the primary outcome among subgroups; age ($\geq$ 65 vs. $<$ 65 years old), sex, NYHA functional class (I-II vs. III-IV), systolic blood pressure ($\geq$ 140 vs. $<$ 140 mmHg), heart rate ($\geq$ 75 vs. $<$ 75 bpm), LVEF ($\geq$ 45 vs. $<$ 45%), atrial fibrillation, anemia, chronic kidney disease (stage 1–2 vs. 3–5), concomitant use of ACEi or ARB.

2.4. Statistical analysis

Patient characteristics, including age, sex, NYHA functional class, duration of HF, vital signs, electrocardiographic findings, echocardiographic findings, comorbidities, laboratory data, and medications were compared with Pearson χ^2 test for categorical variables, Student *t*-test or Wilcoxon rank sum test for continuous variables where applicable and were presented as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR).

A propensity score was estimated by fitting a logistic-regression model which adjusted for age, sex, NYHA functional class (I-II vs. III-IV), duration of HF, systolic blood pressure, diastolic blood pressure, heart rate, hypertension, diabetes mellitus, chronic kidney disease (stage 1–2 vs. 3–5), atrial fibrillation, pacing rhythm, left bundle branch block, LVEF ($<$ 45% vs. $\geq$ 45%), LVDd, digitalis, loop diuretics, thiazides, ACEi or ARB, mineralocorticoid receptor antagonists, amiodarone, and oral inotropes. One-to-one pair matching between the two groups was performed by nearest-neighbor matching without replacement. Covariate balances before and after matching were checked by comparison of standardized mean differences (SMD). A SMD of less than 0.1 was considered to indicate a negligible imbalance between the two groups. Odds ratio (OR) was estimated by logistic regression model and were presented with 95% confidence interval (CI) and *P* value.

Intention-to-treat (ITT) analysis was defined as an analysis of entire matched cohorts. The per-protocol population was defined as patients who received or did not receive beta-blockers both at baseline and 2 years of follow-up. A per-protocol analysis for primary and secondary outcomes was also performed using this per-protocol population.

The analysis of primary and secondary outcomes by using combination of multiple imputation and inverse probability of treatment weighting was also conducted as a sensitivity analysis. [20] For the all missing data at baseline except ALT (due to multicolinearity between AST and ALT), multiple imputation was performed ($n = 10$) by predictive mean matching for continuous variables and logistic regression model for binary variables. A propensity score was estimated by fitting a logistic-regression model which adjusted for all baseline covariates in each dataset. OR for outcomes was estimated by inverse probability weighting. Estimates from 10 iterations were combined with the use of Rubin's rule.

Changes in LVEF, systolic blood pressure, diastolic blood pressure, and heart rate were compared with the use of analysis of covariance (ANCOVA). All tests were 2-tailed, and $P < 0.05$ was considered to be statistically significant. All analyses were performed with the SAS statistical package (version 9.4, SAS Institute, Cary, North Carolina).

2.5. Ethics statement

This study protocol complied with the Declaration of Helsinki. The original study protocol was approved by the Institutional Review Board at Kyushu University. An “opt-out” approach was applied to consent since this study analyzed a nationwide administrative database. The authors had full access to and take full responsibility for the integrity of the data.

3. Results

3.1. Patient characteristics

Fig. 1 shows the method of patient selection in this study. From 2003

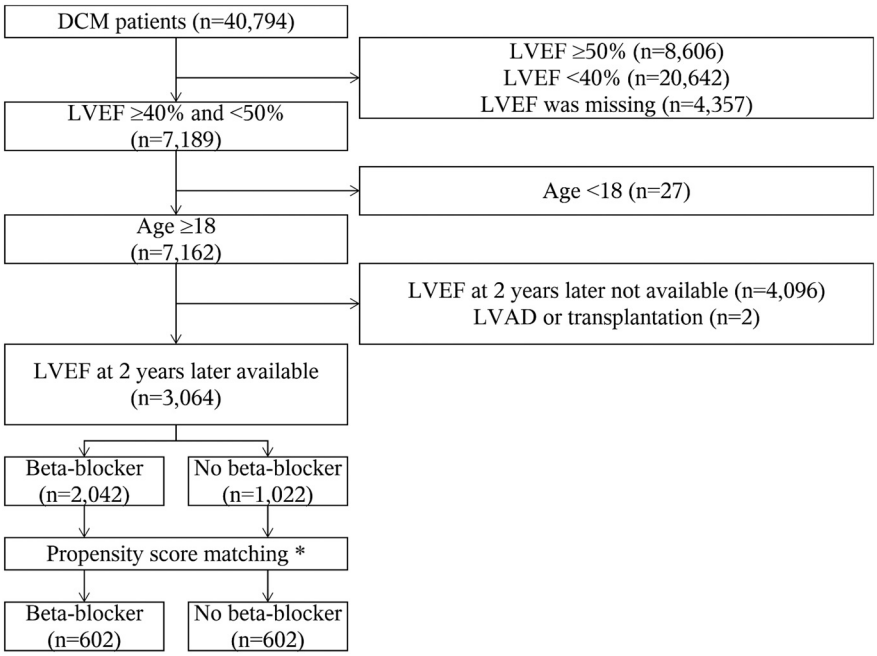

Fig. 1. Patient selection.
DCM, dilated cardiomyopathy; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction.
* Adjusted for age, sex, NYHA functional class (I-II vs. III-IV), duration of HF, systolic blood pressure, diastolic blood pressure, heart rate, hypertension, diabetes mellitus, chronic kidney disease (stage 1–2 vs. 3–5), atrial fibrillation, pacing rhythm, left bundle branch block, LVEF (<45% vs. ≥45%), LVDd, digitalis, loop diuretics, thiazides, ACEi or ARB, mineralocorticoid receptor antagonists, amiodarone, and oral inotropes.

to 2014, 40,794 consecutive patients with DCM were screened and 7162 patients older than 18 years old and with LVEF between 40 and 50% were identified. Two patients who received LVAD or heart transplantation and 4096 patients who were not assessed with echocardiography at 2 years of follow-up were excluded. The remaining 3064 patients were finally included in the present analysis and 2042 patients had beta-blockers. Propensity score matching yielded each 602 patients.

The patient characteristics before and after propensity score matching are shown in Table 1. After propensity score matching, baseline variables were well balanced. In matching cohort, mean age was 59.3 years, 896 (74.4%) was male, and median duration of HF was 5 years. Echocardiography demonstrated that LVEF (44.4 ± 2.9 vs. 44.4 ± 2.9%, SMD = 0.020, $P = 0.73$), LVDd (57.1 ± 7.1 vs. 57.4 ± 7.4 mm, SMD = 0.045, $P = 0.43$), LVDs (44.5 ± 6.1 vs. 44.8 ± 6.5 mm, SMD = 0.049, $P = 0.40$), and the grade III-IV of mitral regurgitation (6.8 vs. 5.3%, SMD = 0.062, $P = 0.36$) were comparable between beta-blocker and no beta-blocker groups.

3.2. Clinical outcomes

Fig. 2 shows primary and secondary outcomes assessed with ITT analysis and per-protocol analysis. The prevalence of an increase in LVEF (24.3 vs. 17.8%; odds ratio [OR] 1.48; 95% confidence interval [CI] 1.12–1.96; $P = 0.006$), and a decrease in LVDs (30.8 vs. 24.7%; OR 1.35; 95% CI 1.04–1.76; $P = 0.023$) were higher in the beta-blocker group. The decrease in LVDd did not reach a statistical significance (17.2 vs. 14.2%; OR 1.26; 95% CI 0.92–1.72; $P = 0.15$). While 564 patients (93.7%) treated with beta-blockers at baseline continued to receive it even at 2 years of follow-up, 480 patients (79.7%) treated without beta-blockers at baseline did not receive it at 2 years of follow-up. The results of per-protocol analysis were compatible with those of ITT analysis (Fig. 2). The increase of LVEF from baseline to 2 years of follow-up was significantly greater in beta-blocker group (2.2 ± 0.4 vs. 0.9 ± 0.4%, $P = 0.037$) (Online Fig. 1a). Changes in systolic and diastolic blood pressure were comparable between groups (Online Fig. 1b and c) Heart rate reduction during the follow-up period was tended to be greater in beta-blocker group (1.33 ± 0.64 vs. 0.61 ± 0.56, $P = 0.069$) (Online Fig. 1d).

Sensitivity analyses are shown in Online Table 1 and Online Fig. 2. Univariate analysis showed that the prevalence of an increase in LVEF (26.7 vs. 19.4%; OR 1.52; 95% CI 1.26–1.82; $P < 0.001$), a decrease in LVDd (20.4 vs. 16.3%; OR 1.32; 95% CI 1.07–1.61; $P = 0.008$), and a decrease in LVDs (35.8 vs. 26.3%; OR 1.56; 95% CI 1.31–1.86; $P < 0.001$) was higher in the beta-blocker group. Combination of multiple imputation and inverse probability of treatment weighting showed that all of the adjusted SMD except thiazides derived from imputed datasets were less than 0.1 and considered to be well-balanced (Online Fig. 2). The prevalence of an increase in LVEF (OR 1.18; 95% CI 1.05–1.33; $P = 0.006$) and a decrease in LVDs (OR 1.19; 95% CI 1.06–1.34; $P = 0.003$) was higher in the beta-blocker group (Online Table 1).

Subgroup analysis demonstrated that patients with heart rate at baseline ≥75 bpm (≥ 75 bpm; OR 2.61; 95% CI 1.66–4.11: < 75 bpm; OR 1.03; 95% CI 0.72–1.48; P for interaction = 0.002) and atrial fibrillation (AF; OR 2.30; 95% CI 1.37–3.86: No AF; OR 1.23; 95% CI 0.88–1.72; P for interaction = 0.046) were benefited by beta-blockers (Fig. 3). The prevalence of an increase in LVEF was higher in the beta-blocker group regardless of NYHA functional class and systolic blood pressure.

The use of ACEi or ARB, digitalis, and CRT at 2 years of follow-up were comparable between the two groups (Online Table 2).

4. Discussion

The present study demonstrated that beta-blockers could induce LVRR among DCM patients with HFmrEF. This effect was significant in subgroups of patients with heart rate ≥ 75 bpm or atrial fibrillation at baseline.

Cleland and colleagues have recently reported a meta-analysis of individual patient data from 11 clinical trials in which the effects of beta-blockers among HFmrEF patients are compared with HFrEF and HFpEF. [14] Beta-blockers were shown to reduce cardiovascular mortality in the subgroup of LVEF 40–50%. [14,15] However, the majority of HFmrEF patients in previous studies had ischemic etiology. Although DCM is a major cause of HF, especially HFmrEF, [18] it remains unknown whether patients with DCM and HFmrEF are similarly benefited by beta-blockers. LVRR is associated with better outcomes in patients with idiopathic DCM. [21] The present study provides the first evidence of effectiveness for LVRR in DCM with HFmrEF.

Although the beneficial effects of beta-blocker on HFrEF seems undisputed, it is the subject of debate whether target heart rate or target

Table 1
Patient characteristics before and after propensity score matching.

Variables	Before propensity score matching				After propensity score matching			
	Beta blocker (n = 2042)	No beta blocker (n = 1022)	SMD	P value	Beta blocker (n = 602)	No beta blocker (n = 602)	SMD	P value
Demographics								
Age, years	56.8 ± 12.7	60.5 ± 12.4	0.289	<0.001	59.2 ± 11.9	59.3 ± 12.3	0.002	0.97
Male	1531 (75.0)	759 (74.3)	0.016	0.67	448 (74.4)	448 (74.4)	0.000	1.00
Duration of HF, years	2.0 (1.0–5.0)	6.0 (2.0–10.0)	0.732	<0.001	5.0 (1.0–9.0)	5.0 (2.0–9.0)	0.029	0.59
NYHA III-IV	261 (13.3)	148 (15.1)	0.052	0.18	89 (14.8)	77 (12.8)	0.058	0.32
Vital signs								
SBP, mm Hg	121.0 ± 19.0	123.7 ± 16.9	0.150	<0.001	122.2 ± 18.3	122.9 ± 16.9	0.040	0.55
DBP, mmHg	73.4 ± 13.7	73.7 ± 11.2	0.022	0.57	73.2 ± 12.4	73.8 ± 11.0	0.053	0.36
HR, bpm	73.1 ± 15.3	73.5 ± 13.9	0.025	0.53	73.0 ± 15.1	73.6 ± 13.8	0.041	0.48
Comorbidities								
Hypertension	108 (5.3)	47 (4.6)	0.032	0.41	31 (5.1)	30 (5.0)	0.008	0.90
Diabetes mellitus	45 (2.2)	28 (2.7)	0.035	0.36	14 (2.3)	15 (2.5)	0.011	0.85
Chronic kidney disease	730 (35.7)	392 (38.4)	0.054	0.16	211 (35.0)	225 (37.4)	0.048	0.40
Laboratory data								
Hemoglobin, g/dl	13.9 ± 1.8	14.0 ± 1.7	0.038	0.34	13.9 ± 1.7	14.0 ± 1.7	0.056	0.35
Albumin, g/dl	4.2 ± 0.4	4.3 ± 0.4	0.115	0.019	4.2 ± 0.4	4.3 ± 0.4	0.055	0.45
AST, U/l	23.0 (19.0–30.0)	23.0 (19.0–30.0)	0.004	0.28	24.0 (19.0–29.0)	24.0 (19.0–30.0)	0.054	0.47
ALT, U/l	22.0 (16.0–33.0)	20.0 (15.0–30.0)	0.134	0.001	22.0 (16.0–33.0)	21.0 (15.0–31.0)	0.119	0.11
Creatinine, mg/dl	0.87 (0.70–1.00)	0.84 (0.70–1.00)	0.018	0.52	0.84 (0.70–1.00)	0.85 (0.70–1.00)	0.045	0.42
Uric acid, mg/dl	6.4 ± 1.8	6.2 ± 1.7	0.113	0.009	6.2 ± 1.7	6.2 ± 1.6	0.012	0.85
Sodium, mEq/l	140.6 ± 2.9	140.8 ± 3.2	0.066	0.23	140.7 ± 3.1	140.7 ± 2.6	0.000	0.93
BNP, pg/ml	58.1 (20.8–180.0)	55.6 (20.9–157.5)	0.128	0.15	63.6 (22.5–190.0)	51.0 (20.4–159.0)	0.093	0.033
Electrocardiographic findings								
Atrial fibrillation	494 (24.2)	319 (31.2)	0.157	<0.001	165 (27.4)	174 (28.9)	0.033	0.56
Pacing	46 (2.3)	12 (1.2)	0.083	0.039	7 (1.2)	8 (1.3)	0.015	0.80
Biventricular pacing	5 (0.2)	1 (0.1)	0.036	0.39	2 (0.3)	0 (0.0)	0.082	0.16
Left bundle branch block	82 (4.0)	31 (3.0)	0.053	0.17	22 (3.7)	20 (3.3)	0.018	0.75
Echocardiographic data								
LVEF, %	44.2 ± 2.9	44.5 ± 2.9	0.099	0.009	44.4 ± 2.9	44.4 ± 2.9	0.020	0.73
LVDd, mm	57.2 ± 6.9	57.2 ± 7.4	0.004	0.92	57.1 ± 7.1	57.4 ± 7.4	0.045	0.43
LVDs, mm	44.6 ± 6.1	44.5 ± 6.4	0.014	0.72	44.5 ± 6.1	44.8 ± 6.5	0.049	0.40
MR III-IV	105 (6.7)	43 (5.9)	0.032	0.48	31 (6.8)	23 (5.3)	0.062	0.36
Medications								
ACEi or ARB	1718 (84.1)	721 (70.5)	0.329	<0.001	475 (78.9)	477 (79.2)	0.008	0.89
MRA	621 (30.4)	192 (18.8)	0.272	<0.001	134 (22.3)	135 (22.4)	0.004	0.94
Loop diuretics	1329 (65.6)	634 (66.9)	0.026	0.50	400 (66.4)	402 (66.8)	0.007	0.90
Thiazides	38 (1.9)	7 (0.7)	0.100	0.019	3 (0.5)	4 (0.7)	0.022	0.70
Digitalis	503 (24.6)	438 (42.9)	0.393	<0.001	221 (36.7)	226 (37.5)	0.017	0.77
Amiodarone	204 (10.0)	51 (5.1)	0.189	<0.001	35 (5.8)	35 (5.8)	0.000	1.00
Oral inotropes	54 (2.6)	44 (4.3)	0.091	0.014	20 (3.3)	23 (3.8)	0.027	0.64

Data are shown as n (percent) or means ± SD otherwise specified.
ACEi, angiotensin-converting-enzyme inhibitors; ARB, angiotensin receptor blockers; BNP, brain-type natriuretic peptide; CKD, chronic kidney disease; DBP, diastolic blood pressure; HF, heart failure; HR, heart rate; LVDd, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonists; SBP, systolic blood pressure; SMD, standardized mean difference.

dose is more important in beta-blocker therapy. While carvedilol has been reported to induce dose-related improvement in LV function and reduction in mortality and hospitalization, [22,23] SHIFT trial showed that patients with heart rate < 75 bpm achieved by beta-blockers had fewer cardiac events than those with heart rate ≥ 75 bpm. [24] A meta-analysis of 23 beta-blocker trials concluded that the magnitude of heart rate reduction is associated with the survival benefit of beta-blockers, whereas the dose of beta-blocker is not. [25] Another meta-analysis of 37 randomized controlled trials of beta-blocker showed the correlation between heart rate reduction and LVEF improvement. [26] High heart rate has been shown to be related to poor outcomes among patients with HFrEF. [27] In the BEAUTIFUL study, the randomized controlled trial of a selective If channel inhibitor, ivabradine, demonstrated that it did not improve cardiac outcomes in all patients with left ventricular systolic dysfunction, but improved outcomes in a subgroup of patients who had heart rates of 70 bpm or greater, [28] SHIFT trial supported the results of the BEUATIFUL study. [29] These findings suggest the importance of heart rate reduction for improvement of clinical outcomes. In the present study, the mean dose of carvedilol was 9.6 mg, which was a half of dose recommended in Japanese Society of Cardiology Guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure. On the other hand, beta-blockers were useful for the patients with DCM and mid-range EF, especially when they had higher heart rate. In addition, heart rate reduction in beta-blocker group tended to be greater than no beta-blocker group (P = 0.069). Although the timing of starting beta-blockers is unknown in the present study, the beneficial effect of beta-blocker in DCM with HFmrEF might be mediated by heart rate reduction.

In the present study, beta-blockers were associated with LVRR in patients with atrial fibrillation. The beneficial effect of beta-blockers on HF patients with atrial fibrillation was controversial. A meta-analysis demonstrated that beta-blockers were not associated with improving prognosis in patients with atrial fibrillation. [30] Another meta-analysis of randomized control trials showed that beta-blockers increased LVEF in patients with atrial fibrillation at baseline who had LVEF of <50%. [14] The magnitude of heart rate reduction was significantly associated with the survival benefit by beta-blockers. [25] The differences of extent of LVRR between sinus rhythm and atrial fibrillation might be explained

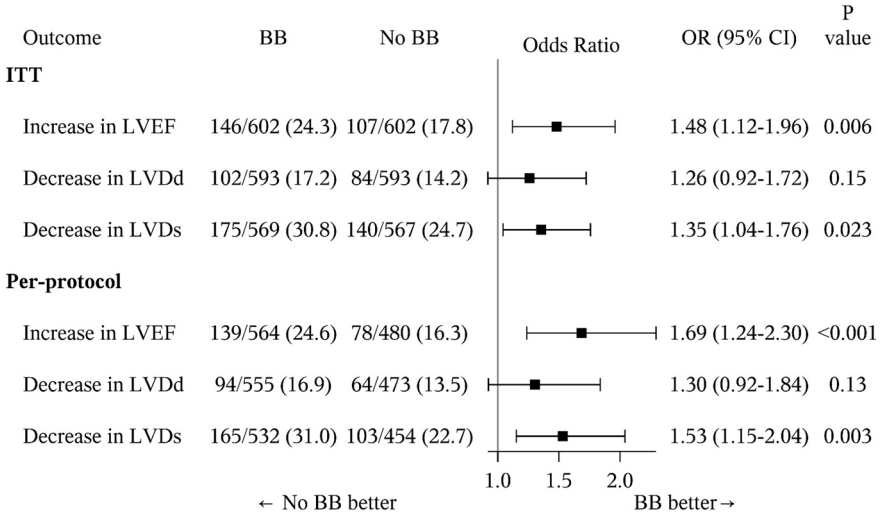

Fig. 2. Primary and secondary outcomes in intention-to-treat analysis and per-protocol analysis.
BB, beta-blockers; CI, confidence interval; ITT, intension-to-treat; LVDd, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; LVEF, left ventricular ejection fraction; OR, odds ratio.

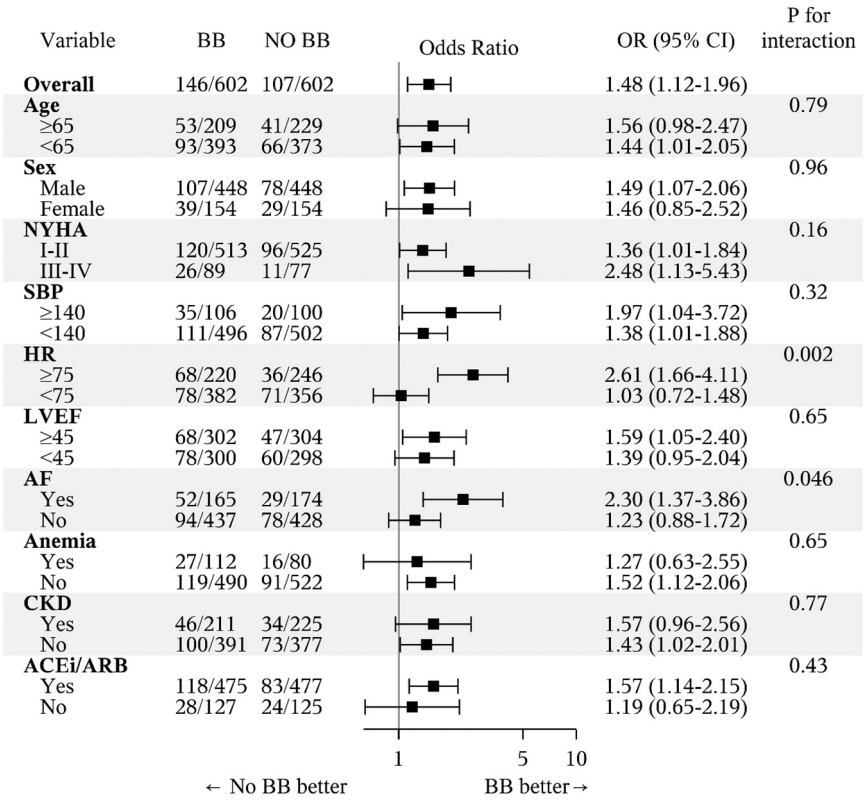

Fig. 3. Subgroup analysis.
ACEi, angiotensin-converting-enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin receptor blockers; BB, beta-blockers; CI, confidence interval; CKD, chronic kidney disease; HR, heart rate; LVEF, left ventricular ejection fraction; OR, odds ratio; SBP, systolic blood pressure.

by the differences of heart rate reduction. Indeed, HR tended to be higher in patients with atrial fibrillation than those with sinus rhythm (data not shown).

HFmrEF includes two dynamic phenotypes, HFrEF-recovered and HFpEF-declined, and HFmrEF dynamically transitions to HFpEF or HFrEF. [15,31,32] Therefore, HFmrEF is thought to represent heterogeneous entity such as a transitional status or an overlap zone between HFpEF and HFrEF. [4,33] The differences in rates of HFrEF-recovered and HFpEF-declined might affect our results because HFrEF-recovered had a more favorable outcome. [34–36] A previous report demonstrated that majority of the patients with HFmrEF had prior LVEF of <40%. [10,37] In the present study, it was not inferred whether study population had HFrEF-recovered or HFpEF-declined because information on prior echocardiography was not collected. To elucidate this crucial issue, further investigations are needed.

4.1. Study limitations

There are several potential limitations to be acknowledged in the present study. First, we did not have the information regarding mortality, cardiovascular event, and rehospitalization due to HF in this study because the clinical personal record did not contain these data. The beneficial effect of beta-blockers in LVRR among DCM patients with HFmrEF might lead to better prognosis. Further studies focusing on this crucial issue are clearly needed in DCM. Second, clinical personal record did not necessitate genetic testing, which might deviate the results. Finally, the present study is retrospective analysis of nationwide database, and despite covariate adjustment, unmeasured factors might have influenced outcomes. Despite several limitations described above, this study analyzed the largest database including more than 3000 DCM patients with HFmrEF and serial echocardiographic data, supporting the conclusion drawn in the present analysis.

5. Conclusions

Beta-blocker use was associated with LVRR in DCM patients with HFmrEF.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Tsutsui 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 Japanese Journal of Clinical Medicine; nonfinancial support from Actelion Pharmaceuticals, Japan Tobacco Inc., Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim, Daiichi-Sankyo, IQVIA Services Japan, and Omron Healthcare Co.; grants from Astellas, Novartis Pharma, Daiichi-Sankyo, Takeda Pharmaceutical, Mitsubishi Tanabe Pharma, and Teijin Pharma, MSD, outside the submitted work. The other authors declare no conflicts of interest associated with this manuscript.

Appendix A. Supplementary data

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