ORIGINAL RESEARCH

Beta-Blocker Use Is Associated With Prevention of Left Ventricular Remodeling in Recovered Dilated Cardiomyopathy

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BACKGROUND: Withdrawal of optimal medical therapy has been reported to relapse cardiac dysfunction in patients with dilated cardiomyopathy (DCM) whose cardiac function had improved. However, it is unknown whether beta-blockers can prevent deterioration of cardiac function in those patients. We examined the effect of beta-blockers on left ventricular ejection fraction (LVEF) in recovered DCM.

METHODS AND RESULTS: We analyzed the clinical personal record of DCM, a national database of the Japanese Ministry of Health, Labor and Welfare, between 2003 and 2014. Recovered DCM was defined as a previously documented LVEF <40% and a current LVEF ≥40%. Patients with recovered DCM were divided into 2 groups according to the use of beta-blockers. A one-to-one propensity case-matched analysis was used. The primary outcome was defined as a decrease in LVEF >10% at 2 years of follow-up. Of 5370 eligible patients, 4104 received beta-blockers. Propensity score matching yielded 1087 pairs. Mean age was 61.9 years, and 1619 (74.5%) were men. Mean LVEF was 49.3±8.2%, and median B-type natriuretic peptide was 46.6 (interquartile range, 18.0–118.1) pg/mL. The primary outcome was observed less frequently in the beta-blocker group than in the no-beta-blocker group (19.6% versus 24.0%; odds ratio [OR], 0.77; 95% CI, 0.63–0.95; P=0.013). Subgroup analysis demonstrated that female patients (women: OR, 0.54; 95% CI, 0.36–0.81; men: OR, 0.88; 95% CI, 0.69–1.12; P for interaction=0.040) were benefited by beta-blockers.

CONCLUSIONS: Beta-blocker use could prevent deterioration of left ventricular systolic function in patients with recovered DCM.

Key Words: beta-blocker ■ dilated cardiomyopathy ■ heart failure with recovered ejection fraction ■ remodeling

A nonnegligible number of patients with heart failure (HF) with reduced ejection fraction (HFrEF) experience recovery of left ventricular ejection fraction (LVEF) as a result of advances in drug therapy, devices, and coronary revascularization.[1] The condition of patients with LVEF ≥40%, who previously had LVEF <40%, was defined as HF with recovered EF (HFrecEF) or HF with improved EF. These patients represent a distinct type of HF, different from HF with preserved EF (HFpEF).[2] Recent studies reported that this type had a better prognosis than HFrEF and HFpEF,[3–5] and the recovery of LVEF is often used as

a surrogate end point in HF clinical trials.[6] However, a quarter of patients with HFrecEF have a subsequent deterioration of LVEF.[7,8] Withdrawal of optimal medical therapy, including beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs), has been reported to result in relapsing cardiac systolic dysfunction in dilated cardiomyopathy (DCM) where LVEF had recovered, referred to as recovered DCM.[9] To the best of our knowledge, the association of beta-blocker use and the changes in LVEF in recovered DCM has not been determined. The aim of this study was to examine

Nonstandard Abbreviations and Acronyms

CRT	cardiac resynchronization therapy
DCM	dilated cardiomyopathy
HFpEF	heart failure with preserved ejection fraction
HFrecEF	heart failure with recovered ejection fraction
HFrEF	heart failure with reduced ejection fraction
LVDD	left ventricular diastolic diameter
NYHA	New York Heart Association
SMD	standardized mean difference

whether the use of beta-blockers could prevent a decrease in LVEF in patients with DCM and LVEF recovery to ≥40%.

METHODS

Patient Database

The clinical personal record, a nationwide administrative database of public expenditure for refractory disease by the Japanese Ministry of Health, Labor and Welfare, was established to register and certify intractable diseases, including cardiomyopathies, throughout Japan. This record prospectively and annually collected the following data: (1) demographic data (age, sex, duration of HF, and New York Heart Association [NYHA] functional class), (2) vital signs, (3) comorbidities, (4) electrocardiographic data, (5) echocardiographic data, (6) laboratory data, and (7) medication use. This database does not collect information about clinical outcomes such as hospitalization and death. 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. The data in this registry were collected from all types of hospitals. All clinical personal records were registered after being reviewed by certified cardiologists. The present study used this nationwide database from 2003 to 2014.

Study Patients

Patients >18 years old with current LVEF ≥40% and previous LVEF <40% were identified from the database of DCM described above. Screened patients were excluded from enrollment if they received a left ventricular assist device 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 the beta-blocker group and those not prescribed were assigned to the no-beta-blocker group. Metoprolol succinate is not available in Japan. All patients had prior symptoms or signs of HF, including dyspnea, palpitation, chest pain, edema, and hepatomegaly.

Outcomes

The primary outcome was defined as a decrease in LVEF ≥10% at 2 years of follow-up, which was one of the outcomes adopted in the TRED-HF (Therapy Withdrawal in Recovered Cardiomyopathy–Heart Failure) study.[9] To evaluate preventive effects of beta-blockers on left ventricular (LV) remodeling, secondary outcomes were an increase in LV diastolic diameter (LVDD) ≥10%[10] and an increase in LV systolic diameter ≥10% at 2 years of follow-up. Echocardiographic data were assessed in each participating hospital. Factors associated with a decrease in LVEF, including systolic blood pressure, diastolic blood pressure, heart rate, atrial fibrillation, use of an ACEI/ARB and digitalis, and cardiac resynchronization therapy (CRT) at 2 years of follow-up, were assessed. We also assessed the primary outcome among subgroups; age (≥65 versus <65 years old), sex, systolic blood pressure (≥120 versus <120 mm Hg), heart rate (≥70

versus <70 bpm), NYHA functional class (I–II versus III–IV), atrial fibrillation, chronic kidney disease (stage 1–2 versus 3–5), and concomitant use of an ACEI or ARB.

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 the Pearson χ^2 test for categorical variables and Student t test or Wilcoxon rank-sum test for continuous variables and were presented as mean±SD or median with interquartile range. To address the possible selection bias, we compared baseline characteristics of eligible patients with those of patients who were not assessed with echocardiography at 2 years of follow-up.

A propensity score was estimated by fitting a logistic-regression model that adjusted for age, sex, duration of HF, NYHA functional class (I–II versus III–IV), atrial fibrillation, pacing rhythm, CRT, LVEF, prior LVEF, hypertension, hyperuricemia, mineralocorticoid receptor antagonists, ACEIs or ARBs, digitalis, and amiodarone. One-to-one pair matching between the 2 groups was performed by nearest-neighbor matching without replacement. Covariate balances before and after matching were checked by comparison of standardized mean difference (SMD). An SMD <0.1 was considered to indicate a negligible imbalance between the 2 groups.

Odds ratio (OR) was estimated by logistic regression model and presented with 95% CI and P value. The number needed to treat to prevent relapse of LVEF <40% at 2 years of follow-up was also calculated. Changes in LVEF were compared with the use of ANCOVA. As duration of HF and LV volume were potential differentiating factors even after propensity score matching, ANCOVA adjusted for LVDD and duration of HF was also conducted.

The per-protocol population was defined as patients who received or did not receive beta-blockers both at baseline and at 2 years of follow-up. A per-protocol analysis was also performed using this per-protocol population.

Considering intra- and interobserver variability of echocardiographic evaluation, we also examined outcomes by multivariable logistic regression model after changing the inclusion criteria as follows: (1) previous LVEF <40% and current LVEF ≥40%, (2) previous LVEF <35% and current LVEF ≥40%, (3) previous LVEF <30% and current LVEF ≥40%, and (4) previous LVEF <40% and current LVEF ≥50%. A decrease in LVEF ≥5%, a decrease in LVEF ≥10%, and a decrease in LVEF ≥15% were also evaluated

as outcomes. Age, sex, duration of HF, NYHA functional class, systolic blood pressure, heart rate, atrial fibrillation, left bundle-branch block, biventricular pacing, LVEF, B-type natriuretic peptide, creatinine, mineralocorticoid receptor antagonists, ACEIs or ARBs, and digitalis were included in the multivariable model. The analysis of outcomes by using a combination of multiple imputation and inverse probability of treatment weighting was also conducted to assess the effects of missing data and selection bias attributable to propensity score matching on outcomes.[11] For the all baseline missing data, 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 that adjusted for all baseline covariates in each data set. OR for outcomes was estimated by inverse probability weighting. Estimates from 10 iterations were combined with the use of Rubin's rule.

A dose-response relationship between delta LVEF and beta-blocker dose was examined by generalized linear regression model adjusted for variables used in multivariable logistic regression model. In this analysis, dose equivalents for carvedilol and bisoprolol were derived from the Japanese Circulation Society Guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure,[12] and 5 mg of bisoprolol was considered to be equivalent to 20 mg of carvedilol. Estimated delta LVEF and carvedilol dose were plotted with the carvedilol dose=0 mg (no-beta-blocker group) as the reference level. Beta-blocker dose standardized in carvedilol units was categorized into 3 groups: 0 mg (no-beta-blocker group), <50% of target dose (<10 mg/day in carvedilol units), and ≥50% of target dose (≥10 mg/day in carvedilol units). The association between each outcome and categorized beta-blocker dose was examined by multivariable logistic regression model using same covariates stated above.

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, NC). The authors had full access to and take full responsibility for the integrity of the data.

Ethics Statements

This study protocol was organized to ensure compliance with the Declaration of Helsinki. The original study protocol was approved by the Institutional Review Board at Kyushu University. Since this study analyzed a nationwide administrative database, the "opt-out" principle was applied. The data that support the findings of this study are available from the corresponding author upon reasonable request.

RESULTS

Patient Characteristics

Figure 1 shows the method of patient selection in this study. From 2003 to 2014, 40 794 consecutive patients with DCM were screened, and 10 107 patients were identified as recovered DCM, of which 5422 patients were assessed with echocardiography 2 years later. Twenty-three patients <18 years old and 28 patients who received left ventricular assist device or heart transplantation were excluded. The remaining 5370 patients were finally included in the present analysis, and 4104 patients were on beta-blockers. Propensity score matching yielded each 1087 patients.

In comparison with patients who were not assessed with echocardiography at 2 years of follow-up, eligible patients had slightly lower B-type natriuretic peptide (40.0 [13.8–106.0] versus 41.8 [14.6–118.0] pg/mL; P=0.006; SMD=0.109), higher prior LVEF (29.2±7.4% versus 28.2±7.5%; P<0.001; SMD=0.132), and a higher prescription rate of ACEIs/ARBs (81.1% versus 75.1%; P<0.001; SMD=0.147) (Table S1). However, overall baseline characteristics, including these variables, were clinically comparable.

Patient characteristics before and after propensity score matching are shown in Table 1. After propensity score matching, variables were considered to be well balanced. In a matching cohort, mean age was 61.9 years, 1619 (74.5%) were men, and median duration of HF was 7 years. Echocardiography

demonstrated that LVEF (49.4±8.4% versus 49.2±8.0%; P=0.56; SMD=0.025), LVDD (55.7±7.8 versus 56.0±8.0 mm; P=0.36; SMD=0.040), LV systolic diameter (41.7±7.9 versus 42.1±7.8 mm; P=0.26; SMD=0.050), and grade III to IV mitral regurgitation (7.0% versus 6.7%; P=0.79; SMD=0.013) were comparable between the beta-blocker and no-beta-blocker groups. Previous LVEF was also comparable (30.4±7.1% versus 30.6±7.0%; P=0.57; SMD=0.024). In the beta-blocker group, the beta-blocker dose standardized in carvedilol units was 10.0 (5.0–15.0) mg/day at baseline and 10.0 (5.0–15.0) mg/day at 2 years of follow-up.

Clinical Outcomes

Figure 2 shows primary and secondary outcomes. The prevalence of decrease in LVEF in the beta-blocker group was lower than that in the no-beta-blocker group (19.6% versus 24.0%; OR, 0.77; 95% CI, 0.63–0.95; P=0.013) in intention-to-treat analysis (Figure 2A). The prevalence of increase in LVDD (11.7% versus 15.7%; OR, 0.71; 95% CI, 0.55–0.92; P=0.008) was also lower in the beta-blocker group (Figure 2B). The prevalence of increase in LV systolic diameter tended to be lower in the beta-blocker group (Figure 2C).

In the beta-blocker group, 1017 patients (93.6%) continued to receive beta-blockers at 2 years of follow-up. On the other hand, in the no-beta-blocker group, 835 patients (76.8%) did not receive it even at 2 years of follow-up. Per-protocol analysis also
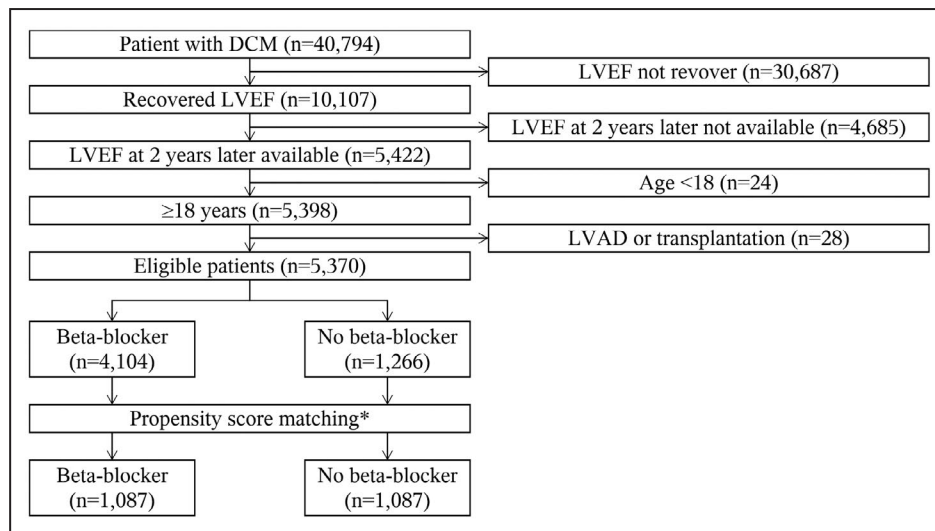
Figure 1. Patient selection.
DCM indicates dilated cardiomyopathy; LVAD, left ventricular assist device; and LVEF, left ventricular ejection fraction. *Adjusted for age, sex, duration of heart failure, New York Heart Association functional class (I–II vs III–IV), atrial fibrillation, pacing rhythm, cardiac resynchronization therapy, LVEF, prior LVEF, hypertension, hyperuricemia, mineralocorticoid receptor antagonists, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, digitalis, and amiodarone.

Table 1. Patient Characteristics

Variables	Before Propensity Score Matching				After Propensity Score Matching			
	Beta-Blocker (n=4104)	No-Beta-Blocker (n=1266)	SMD	P Value	Beta-Blocker (n=1087)	No-Beta-Blocker (n=1087)	SMD	P Value
Demographics								
Age, y	58.4±12.9	62.2±12.7	0.301	<0.001	61.9±12.2	62.0±12.7	0.006	0.90
Male patients	3134 (76.4)	941 (74.3)	0.047	0.14	815 (75.0)	804 (74.0)	0.023	0.59
Duration of HF, y	4.0 (2.0–7.0)	8.0 (3.0–10.0)	0.574	<0.001	6.0 (3.0–10.0)	7.0 (3.0–10.0)	0.045	0.20
NYHA functional class								
I–II	3615 (92.2)	1047 (86.5)	0.186	<0.001	960 (88.3)	951 (87.5)	0.025	0.55
III–IV	304 (7.8)	163 (13.5)	0.186	<0.001	127 (11.7)	136 (12.5)	0.025	0.55
Vital signs								
SBP, mm Hg	120.1±17.8	121.3±17.6	0.068	0.038	120.9±17.5	121.2±17.8	0.017	0.72
DBP, mm Hg	71.9±12.5	71.7±11.6	0.016	0.62	71.7±12.3	71.7±11.6	0.004	0.93
Heart rate, bpm	71.4±11.9	72.2±12.8	0.067	0.055	71.4±11.9	71.9±12.5	0.042	0.35
Comorbidities								
Hypertension	443 (10.8)	95 (7.5)	0.114	<0.001	98 (9.0)	86 (7.9)	0.040	0.36
Diabetes mellitus	191 (4.7)	59 (4.7)	0.000	0.99	60 (5.5)	49 (4.5)	0.046	0.28
CKD stage 3–5	1656 (40.4)	547 (43.2)	0.058	0.071	469 (43.2)	455 (41.9)	0.026	0.54
Hyperuricemia	1745 (42.5)	437 (34.5)	0.165	<0.001	378 (34.8)	374 (34.4)	0.008	0.86
Laboratory data								
Hemoglobin, g/dL	13.8±1.8	13.6±1.8	0.085	0.010	13.7±1.8	13.6±1.8	0.015	0.74
Albumin, g/dL	4.3±0.4	4.2±0.4	0.053	0.20	4.2±0.4	4.2±0.4	0.028	0.62
AST, U/L	22.0 (18.0–29.0)	23.0 (19.0–30.0)	0.008	0.005	22.0 (18.0–29.0)	23.0 (19.0–30.0)	0.004	0.019
ALT, U/L	21.0 (15.0–30.0)	20.0 (15.0–31.0)	0.010	0.97	20.0 (15.0–29.0)	21.0 (15.0–31.0)	0.087	0.090
Creatinine, mg/dL	0.89 (0.75–1.06)	0.89 (0.75–1.05)	0.002	0.70	0.88 (0.74–1.09)	0.89 (0.74–1.05)	0.038	0.92
eGFR, mL/min per 1.73 m^2	68.0±36.1	65.7±33.9	0.067	0.038	66.9±39.3	66.3±35.5	0.014	0.74
Uric acid, mg/dL	6.4±1.7	6.2±1.8	0.090	0.011	6.2±1.7	6.2±1.7	0.010	0.82
Sodium, mEq/L	140.5±2.8	140.6±3.2	0.033	0.76	140.6±3.0	140.5±3.1	0.033	0.43
BNP, pg/mL	38.5 (13.0–102.8)	44.6 (18.1–114.0)	0.076	0.002	50.5 (17.7–120.7)	44.4 (18.3–115.5)	0.013	0.31
Electrocardiographic findings								
Atrial fibrillation	877 (21.4)	351 (27.7)	0.148	<0.001	314 (28.9)	307 (28.2)	0.014	0.74
Pacing	167 (4.1)	36 (2.8)	0.067	0.046	23 (2.1)	28 (2.6)	0.030	0.48
Biventricular pacing	50 (1.2)	4 (0.3)	0.104	0.005	5 (0.5)	3 (0.3)	0.030	0.48
Left bundle-branch block	86 (2.1)	26 (2.1)	0.003	0.93	27 (2.5)	26 (2.4)	0.006	0.89
Echocardiographic data								
LVEF, %	50.0±8.5	49.2±8.0	0.095	0.003	49.4±8.4	49.2±8.0	0.025	0.56
Prior LVEF, %	28.8±7.4	30.6±7.1	0.244	<0.001	30.4±7.1	30.6±7.0	0.024	0.57
LVDD, mm	55.4±7.7	55.9±8.1	0.069	0.036	55.7±7.8	56.0±8.0	0.040	0.36
LVDS, mm	41.3±7.8	42.1±7.9	0.097	0.003	41.7±7.9	42.1±7.8	0.050	0.26
MR III–IV	146 (4.6)	66 (7.0)	0.101	0.004	59 (7.0)	55 (6.7)	0.013	0.79
Medication								
Carvedilol	3833 (93.4)	…	…	…	1012 (93.1)	…	…	…
Dose of carvedilol, mg	10.0 (7.5–15.0)	…	…	…	10.0 (5.0–15.0)	…	…	…
Bisoprolol	281 (6.9)	…	…	…	78 (7.2)	…	…	…
Dose of bisoprolol, mg	5.0 (2.5–5.0)	…	…	…	5.0 (2.5–5.0)	…	…	…

(Continued)

Table 1. Continued

Variables	Before Propensity Score Matching				After Propensity Score Matching			
	Beta-Blocker (n=4104)	No-Beta-Blocker (n=1266)	SMD	P Value	Beta-Blocker (n=1087)	No-Beta-Blocker (n=1087)	SMD	P Value
Beta-blocker dose standardized in carvedilol units, mg	10.0 (7.5–20.0)	…	…	…	10.0 (5.0–15.0)	…	…	…
ACEIs or ARBs	3528 (86.0)	828 (65.4)	0.494	<0.001	796 (73.2)	767 (70.6)	0.059	0.17
MRA	1532 (37.3)	308 (24.3)	0.284	<0.001	295 (27.1)	283 (26.0)	0.025	0.56
Loop diuretics	2880 (70.9)	715 (63.8)	0.150	<0.001	758 (69.9)	652 (68.6)	0.030	0.50
Thiazides	133 (3.3)	25 (2.8)	0.034	0.37	31 (2.9)	23 (3.1)	0.010	0.84
Digitalis	1087 (27.2)	484 (41.2)	0.298	<0.001	419 (38.6)	436 (40.1)	0.032	0.46
Amiodarone	501 (12.2)	86 (6.8)	0.185	<0.001	90 (8.3)	74 (6.8)	0.056	0.19
Oral inotropes	166 (4.0)	54 (4.3)	0.011	0.73	50 (4.6)	46 (4.2)	0.018	0.68

Data are shown as n (percent), means±SD, or median (interquartile range) otherwise specified. ACEI indicates angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; 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; and SMD, standardized mean difference.

showed that beta-blockers reduced the prevalence of increases in LVEF (19.2% versus 24.0%; OR, 0.75; 95% CI, 0.60–0.94; *P*=0.013) (Figure 2D) and LVDD (11.4% versus 15.4%; OR, 0.71; 95% CI, 0.54–0.93; *P*=0.013) (Figure 2E). Beta-blockers tended to reduce the prevalence of increase in LV systolic diameter (Figure 2F).

Sensitivity analyses are shown in Table 2. The prevalence of decrease in LVEF ≥5%, ≥10%, and ≥15% was lower in the beta-blocker group in all data sets after changing the inclusion criteria. A combination of multiple imputation and inverse probability of treatment weighting showed that all of the adjusted SMDs derived from the imputed data set were <0.1 and considered to be well balanced (Figure S1). The prevalence of decrease in LVEF ≥5%, ≥10%, and ≥15% was also lower in the beta-blocker group (Table 2).

Subgroup analysis demonstrated that female patients (women: OR, 0.54; 95% CI, 0.36–0.81; men: OR, 0.88; 95% CI, 0.69–1.12; *P* for interaction=0.040) were benefited by beta-blockers (Figure 3).

As a result of preventing a decrease in LVEF, the deterioration to LVEF <40% in recovered DCM was also prevented by the use of beta-blockers (24.2% versus 30.4%; *P*=0.003) (Figure 4). The number needed to treat to prevent relapse of LVEF <40% at 2 years of follow-up was 16.1. In addition, the changes of LVEF from baseline to 2 years of follow-up in the beta-blocker and no-beta-blocker groups were −1.9±0.3% and −3.3±0.3% in overall matched patients (*P*=0.002), −3.2±0.6% and −6.0±0.6% in patients with baseline LVEF ≥50% (*P*<0.001), and −1.1±0.4% and −1.5±0.4% in patients with baseline LVEF <50% (*P*=0.44) (Table 3). After adjusting for LVDD and duration of HF, beta-blockers were also associated with prevention of decrease in LVEF in overall matched patients (*P*=0.004)

and patients with baseline LVEF ≥50% (*P*<0.001). Dose-response relationship between delta LVEF and beta-blocker are shown in Figure 5. The beneficial effects of beta-blockers on LVEF increased in a dose-dependent manner. Taking ≥50% of the target dose of beta-blockers was consistently associated with prevention of decrease in LVEF (Table S2).

Systolic blood pressure, diastolic blood pressure, heart rate, atrial fibrillation, and the use of ACEIs or ARBs and digitalis at 2 years of follow-up were comparable between the 2 groups (Table 4). The beta-blocker group received biventricular pacing more frequently at 2 years of follow-up (1.1% versus 0.4%; *P*=0.045), but it was considered to be less clinically significant.

DISCUSSION

The major finding of the present study was that the use of beta-blockers was associated with prevention of a decrease in LVEF during 2 years of follow-up in patients with recovered DCM. The decrease in LVEF was mitigated in a dose-dependent manner. This is the first report exclusively focusing on the importance of beta-blockers in preventing relapse of recovered DCM.

HFpEF-improved or HFrecEF, which was recognized as a subset of patients with HFpEF who previously had HFrEF,[13] was first proposed in 2013 American College of Cardiology/American Heart Association guidelines[2,14] because these patients appeared to be clinically distinct from patients with HFpEF or HFrEF. Beta-blockers, mineralocorticoid receptor antagonists, and CRT have been shown to induce LV reverse remodeling in a substantial proportion of patients with HFrEF.[4,7,15–17] IMPROVE HF (Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the
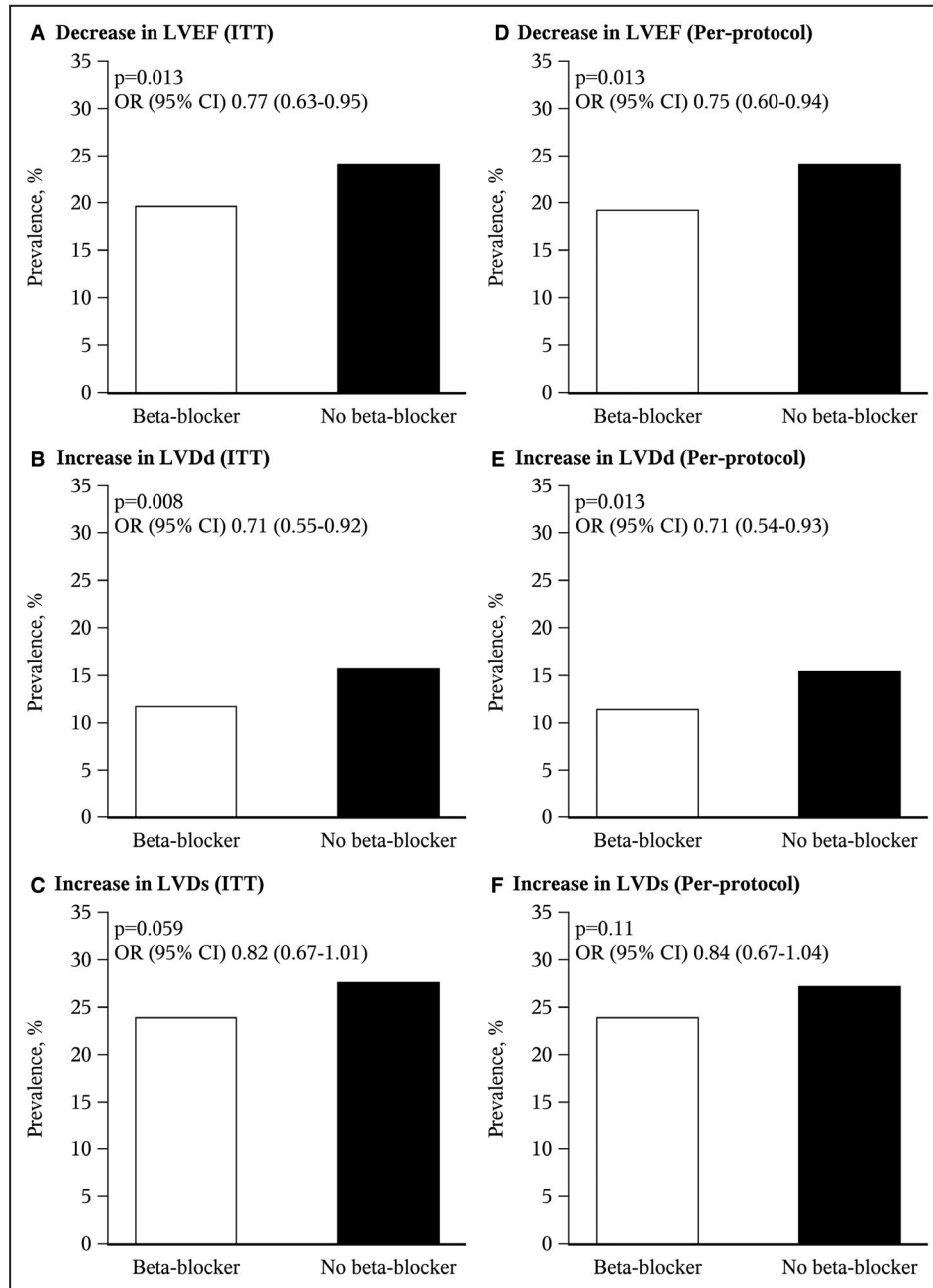
Figure 2. Primary and secondary outcomes.
Primary outcome and increase in LVDD was less frequently observed in the beta-blocker group both in ITT and per-protocol analysis (**A**, **B**, **D**, and **E**). Increase in LVDS was more frequently observed in ITT analysis, but it did not reach a statistical significance in per-protocol analysis (**C** and **F**). ITT indicates intention-to-treat analysis; LVDD, left ventricular diastolic diameter; LVDS, left ventricular systolic diameter; LVEF, left ventricular ejection fraction; and OR, odds ratio.

Outpatient Setting) also demonstrated that one-third of the outpatients with HF had a >10% improvement in LVEF at 24 months by guideline-recommended therapies for HF.[16] Previous studies showed that patients with HFrecEF were younger, with a lower prevalence of coronary artery disease, hypertension, diabetes mellitus, and atrial fibrillation, with a better renal function, and were more likely to be treated with beta-blockers

or ACEIs.[2–4] Patient characteristics in our study were consistent with these previous studies.

In the Val-HeFT (Valsartan Heart Failure Trial), HFrecEF demonstrated a more favorable outcome compared with persistently reduced EF.[3] Another retrospective cohort study showed that patients with HFrecEF had lower rates of all-cause mortality, cardiovascular mortality, and hospitalizations attributable

Table 2.   Sensitivity Analyses

Data Set	Outcome	OR (95% CI)	P Value
Prior LVEF <40% Current LVEF ≥40%	Reduction in LVEF ≥5%	0.71 (0.59–0.86)	<0.001
	Reduction in LVEF ≥10%	0.73 (0.59–0.91)	0.005
	Reduction in LVEF ≥15%	0.60 (0.45–0.78)	<0.001
Prior LVEF <35% Current LVEF ≥40%	Reduction in LVEF ≥5%	0.66 (0.53–0.83)	<0.001
	Reduction in LVEF ≥10%	0.67 (0.52–0.88)	0.003
	Reduction in LVEF ≥15%	0.57 (0.41–0.80)	0.001
Prior LVEF <30% Current LVEF ≥40%	Reduction in LVEF ≥5%	0.68 (0.51–0.92)	0.012
	Reduction in LVEF ≥10%	0.64 (0.46–0.90)	0.011
	Reduction in LVEF ≥15%	0.56 (0.37–0.84)	0.005
Prior LVEF <40% Current LVEF ≥50%	Reduction in LVEF ≥5%	0.61 (0.46–0.81)	<0.001
	Reduction in LVEF ≥10%	0.61 (0.44–0.84)	0.003
	Reduction in LVEF ≥15%	0.53 (0.36–0.77)	<0.001
Imputed data set	Reduction in LVEF ≥5%	0.76 (0.70–0.82)	<0.001
	Reduction in LVEF ≥10%	0.82 (0.74–0.90)	<0.001
	Reduction in LVEF ≥15%	0.69 (0.61–0.79)	<0.001

Beta-blocker use was consistently associated with the prevention of deterioration in LVEF in recovered DCM. LVEF indicates left ventricular ejection fraction; and OR, odds ratio.

to HF.[4] However, a quarter of patients with HFrecEF experience a subsequent deterioration of LVEF, and these patients are at higher risk of cardiovascular mortality.[7] In a prospective cohort study of 1821 patients with chronic HF, HFrecEF was associated with a better biomarker profile and event-free survival than HFrEF and HFpEF. However, these patients still had abnormalities in biomarkers and a significant number of HF hospitalizations.[18] It has been suggested that one of the mechanisms responsible for recurrent HF events in patients with HFrecEF relates to incomplete reversal of the HF phenotype that arises secondary to irreversible
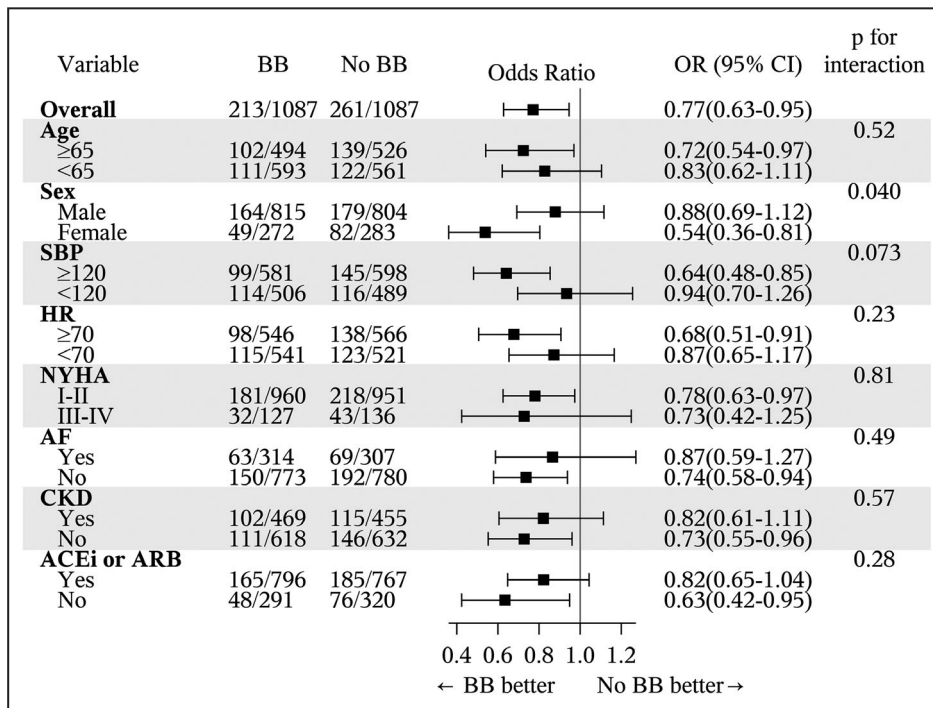

Figure 3.   Subgroup analysis of the primary outcome.
Female patients were more benefited by beta-blockers. ACEI indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BB, beta-blocker; CKD, chronic kidney disease; HR, heart rate; OR, odds ratio; and SBP, systolic blood pressure.
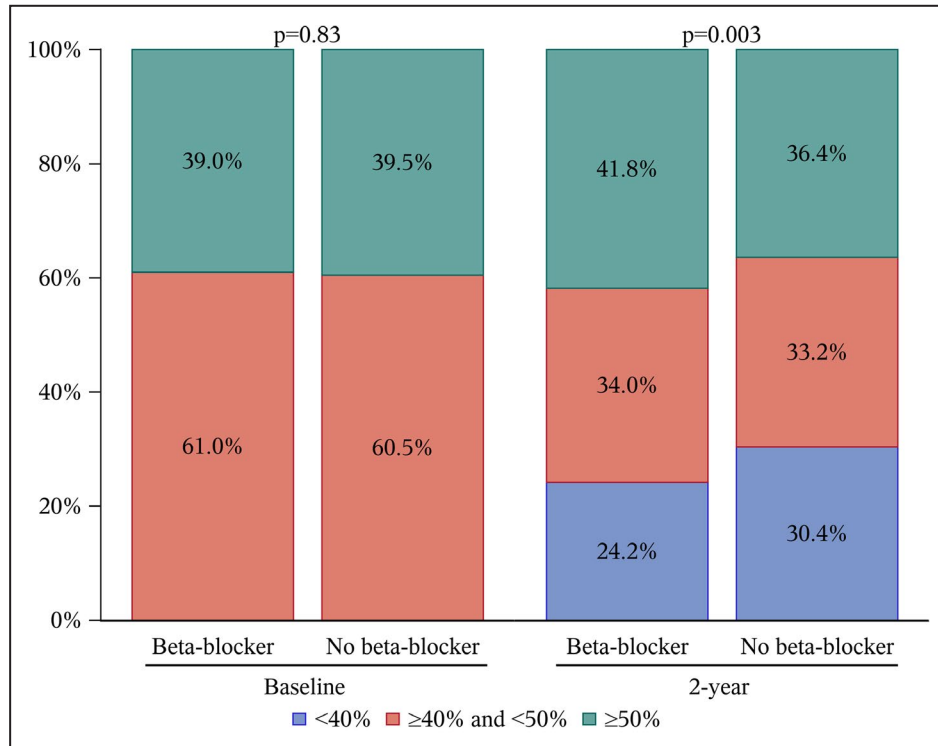
Figure 4. Changes in the types of heart failure according to beta-blocker use.
Beta-blocker was associated with lower prevalence of LVEF <40% at follow-up. LVEF indicates left ventricular ejection fraction.

end-organ myocardial damage in the failing heart.[19] These studies have indicated that optimal therapeutic strategy needs to be established for HFrecEF.

Swedberg et al demonstrated that withdrawal of beta-blockers in 15 patients with congestive HF who had recovered from systolic LV dysfunction caused a significant decrease in LVEF, which was improved within a few weeks to months after readministration of beta-blockers.[20] In a retrospective cohort study of 42 patients with recovered DCM, recurrence of LV dysfunction was correlated with the discontinuation of HF medications.[21] The TRED-HF open-label, pilot, randomized trial, examined the effects of phased

withdrawal of HF medications in patients with recovered DCM and showed that 44% of these patients met the primary outcome, defined by a decrease in LVEF of >10% and <50%, an increase in LV end-diastolic volume of 10%, a 2-fold rise in N-terminal pro-B-type natriuretic peptide to >400 ng/L, or clinical evidence of HF.[9] The present study focused on beta-blockers and LV function and demonstrated the first evidence regarding ameliorating effects of beta-blockers on a decrease in LVEF in patients with recovered DCM. Beta-blockers attenuated not only a decrease in the LVEF but also an increase in LVDD, suggesting their preventive effects on recurrence of LV remodeling.

Table 3. ANCOVA for Change in LVEF

Group	Variable	Baseline	Change	P Value	
				Effect of Beta-blocker	Effect of Baseline LVEF
Overall	Beta-blocker	49.4±8.4	−1.9±0.3	0.002	<0.001
	No-beta-blocker	49.2±8.0	−3.3±0.3		
LVEF ≥50%	Beta-blocker	57.9±6.8	−3.2±0.6	<0.001	<0.001
	No-beta-blocker	57.3±6.3	−6.0±0.6		
LVEF <50%	Beta-blocker	44.0±2.9	−1.1±0.4	0.44	<0.001
	No-beta-blocker	43.9±2.9	−1.5±0.4		

Beta-blocker use was associated with the prevention of deterioration in LVEF in recovered DCM. LVEF indicates left ventricular ejection fraction.
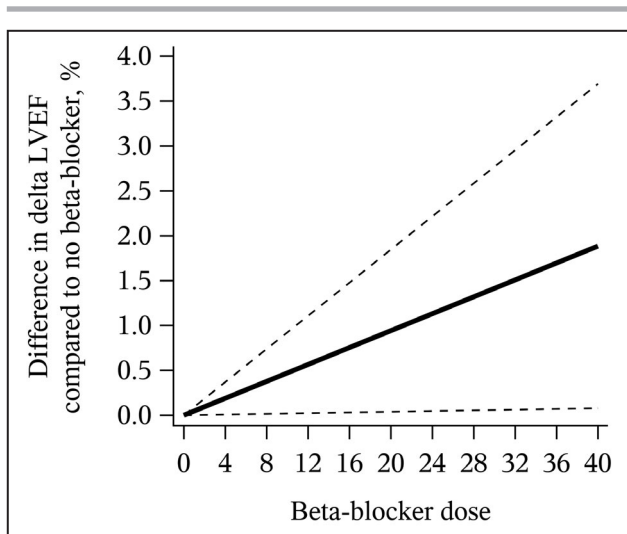
Figure 5. Dose-response relationship between delta LVEF and dose of beta-blocker.
Beta-blockers prevented a decrease in LVEF as beta-blocker dose increased. Solid line represents estimated delta LVEF with the carvedilol dose=0 mg as the reference level and dotted line does 95% CI. LVEF indicates left ventricular ejection fraction.

Absolute difference in delta LVEF between groups was small (2.4% in patients with LVEF ≥50% and 0.9% in LVEF between 40% and 50%). Previous studies showed that change in LVEF in response to carvedilol compared with placebo was 5% to 8% in patients with HFrEF.[22–24] One possible reason for this discrepancy is that 60% of the patients had HFmrEF, and around half of the patients did not experience a decrease or increase in LVEF in this study. Although a dose-response relationship between delta LVEF and beta-blockers was observed, median carvedilol dose was 10 mg. It was half of the dose recommended in the Japanese Circulation Society Guideline. This also accounted for a modest change in LVEF by beta-blockers. However,

Table 4. Vital Signs, Atrial Fibrillation, Medications, and Beventricular Pacing at 2 Years of Follow-Up

Variables	Beta-Blocker (n=1087)	No-Beta-Blocker (n=1087)	P Value
Systolic blood pressure, mm Hg	118.9±17.5	119.7±17.5	0.27
Diastolic blood pressure, mm Hg	70.6±11.5	71.1±11.7	0.37
Heart rate, bpm	71.8±12.3	72.6±13.0	0.16
Atrial fibrillation, n (%)	294 (27.1)	310 (28.5)	0.44
Left bundle-branch block, n (%)	29 (2.7)	29 (2.7)	1.00
ACEI/ARB, n (%)	786 (72.5)	803 (73.9)	0.45
Digitalis, n (%)	374 (36.4)	411 (39.8)	0.11
Biventricular pacing, n (%)	12 (1.1)	4 (0.4)	0.045

Vital signs, atrial fibrillation, medications, and biventricular pacing at 2 years of follow-up did not differ between groups. ACEI indicates angiotensin-converting enzyme inhibitor; and ARB, angiotensin receptor blocker.

beta-blockers prevented a decrease in LVEF ≥5%, ≥10%, and ≥15% and transition to HFrEF, which represent clinically relevant differences.

In the subgroup analysis, female patients benefited more than male patients (Figure 3). Ghimire et al[25] demonstrated that female patients exhibited lower mortality than men in HFrecEF. Combined with our results, female patients are likely to benefit from optimal medical therapy, which leads to a better prognosis. Further studies were warranted to investigate sex differences in this entity.

There are other factors possibly associated with LVEF decline in HFrecEF. Digitalis withdrawal were known to be related to LVEF decline.[26] In the retrospective cohort study of 174 patients with HFrecEF, the patients with a complete left bundle-branch block had subsequent LVEF deterioration compared with those without it (hazard ratio, 3.52; 95% CI, 1.34–9.26; P=0.01).[7] CRT induced LV reverse remodeling and the benefit was lost gradually 4 weeks after withholding pacing.[27] In the present study, the use of digitalis or left bundle-branch block both at baseline and at 2 years of follow-up were similar between groups (Tables 1 and 4). The implantation rate of CRT was quite low and comparable between groups at baseline as well as 2 years of follow-up (Tables 1 and 4). Other clinically relevant variables, including blood pressure, heart rate, atrial fibrillation, and ACEIs/ARBs at 2 years of follow-up, were also comparable (Table 4). These findings indicate that the difference in LVEF decline in the 2 groups was independent of these factors.

To further confirm the effect of beta-blockers on prevention of LV remodeling in recovered DCM, a prospective randomized study is needed. However, it is ethically difficult not to administrate beta-blockers in such patients for a long time in a prospective study. The findings from large-scale data analysis like this observational study are clinically important.

Taken together, even though LVEF is fully recovered, periodic echocardiographic assessment is required, and beta-blockers must be continued indefinitely in patients with DCM.

Study Limitations

There are several potential limitations to be acknowledged in the present study. First, we did not have information regarding mortality, cardiovascular event, and hospitalization attributable to HF in this study because the clinical personal record did not contain these data. It is a crucial issue that the preventive effect of beta-blockers against LV remodeling could be related to survival or other events in patients with recovered DCM. Further studies focusing on this important issue are needed. Second, this database does not include information regarding genetic testing or late gadolinium

enhancement in cardiac magnetic resonance imaging. It has been reported that patients with DCM harboring titin truncating variants have better prognosis than those with lamin A/C variants[28] and late gadolinium enhancement is an independent predictor for LV remodeling in DCM.[29–31] These might affect results in this study. Third, echocardiographic assessment was not adjudicated. However, the diagnosis of HFrEF (LVEF <40%) was validated by certified cardiologists. Fourth, the reason why some patients did not receive beta-blockers, such as patient's request, bradycardia, and comorbidities, including asthma or chronic obstructive pulmonary disease, could not be inferred. It is unlikely that beta-blockers were discontinued because of bradycardia, as heart rate in the no-beta-blocker group was not so low (71.9±12.7 bpm). Asthma and chronic obstructive pulmonary disease might affect the mortality but be less likely to affect LV function. Fifth, of 10 107 patients with HFrecEF, 4685 patients were excluded because they were not assessed with echocardiography at 2 years of follow-up. Although the baseline characteristics of eligible patients and patients who were not assessed with echocardiography at 2 years of follow-up were almost comparable (Table S1), patient selection bias has not been completely excluded. It was less likely to affect the generalizability. Sixth, the present study is not a prospective randomized trial, and unmeasured factors might have influenced the outcomes. In addition, confounding by indication is not be completely excluded. However, we performed several sensitivity analyses and validated the effects of beta-blockers on LVEF.

Despite several limitations described above, we analyzed the largest database that included more than 40 000 patients with DCM and serial echocardiographic data, supporting the conclusion drawn in the present study.

CONCLUSIONS

Beta-blocker use is associated with the prevention of deterioration in LVEF in recovered DCM.

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Supplemental Material

Table S1. Characteristics of eligible patients and patients who were not assessed with echocardiography at 2-year follow-up.

Variables	Eligible (n = 5370)	Missing (n = 4665)	SMD	P value
Demographics				
Age, years	59.3 ± 12.9	59.9 ± 13.9	0.045	0.026
Male	4075 (75.9)	3496 (74.9)	0.022	0.27
Duration of HF, years	4.0 (2.0-9.0)	4.0 (2.0-9.0)	0.031	0.011
NYHA				
I-II	4662 (90.9)	3940 (88.7)	0.073	<0.001
III-IV	467 (9.1)	502 (11.3)	0.073	<0.001
Vital signs				
SBP, mmHg	120.4 ± 17.7	119.7 ± 17.7	0.040	0.087
DBP, mmHg	71.9 ± 12.3	71.8 ± 12.9	0.006	0.78
Heart rate, bpm	71.6 ± 12.1	72.6 ± 12.6	0.087	<0.001
Comorbidities				
Hypertension	538 (10.0)	492 (10.6)	0.017	0.39
Diabetes mellitus	250 (4.7)	217 (4.7)	0.000	0.99
CKD stage 3-5	2203 (41.0)	2012 (43.1)	0.043	0.033
Hyperuricemia	2182 (40.6)	1912 (41.0)	0.007	0.72
Laboratory data				
Hemoglobin, g/dl	13.7 ± 1.8	13.5 ± 1.9	0.102	<0.001
Albumin, g/dl	4.2 ± 0.4	4.2 ± 0.4	0.129	<0.001
AST, U/l	22.0 (18.0-29.0)	22.0 (18.0-29.0)	0.021	0.32
ALT, U/l	21.0 (15.0-30.0)	20.0 (14.0-29.0)	0.018	0.003
Creatinine, mg/dl	0.89 (0.75-1.06)	0.90 (0.75-1.10)	0.057	0.014
eGFR, ml/min/1.73m^2	67.49 ± 35.61	66.21 ± 34.82	0.036	0.076
Uric acid, mg/dl	6.3 ± 1.7	6.4 ± 1.7	0.020	0.36
Sodium, mEq/l	140.5 ± 2.9	140.2 ± 3.1	0.101	<0.001
BNP, pg/ml	40.0 (13.8-106.0)	41.8 (14.6-118.0)	0.109	0.006
Electrocardiographic findings				
Atrial fibrillation	1228 (22.9)	941 (20.2)	0.066	0.001

Pacing	203 (3.8)	193 (4.1)	0.018	0.36
Biventricular pacing	54 (1.0)	32 (0.7)	0.035	0.083
Left bundle branch block	112 (2.1)	93 (2.0)	0.007	0.75
Echocardiographic data				
LVEF, %	49.8 ± 8.4	49.8 ± 8.6	0.000	0.99
Prior LVEF, %	29.2 ± 7.4	28.2 ± 7.5	0.132	<0.001
LVDd, mm	55.5 ± 7.8	55.2 ± 8.0	0.040	0.046
LVDs, mm	41.5 ± 7.8	41.4 ± 8.2	0.003	0.90
MR III-IV	212 (5.2)	222 (6.3)	0.049	0.033
Medication				
Carvedilol	3833 (71.4)	3202 (68.7)	0.058	0.004
Dose of carvedilol, mg	10.0 (7.5-15.0)	10.0 (5.0-20.0)	0.023	0.77
Bisoprolol	281 (5.2)	398 (8.5)	0.131	<0.001
Dose of bisoprolol, mg	5.0 (2.5-5.0)	2.5 (2.5-5.0)	0.184	0.006
Beta-blocker dose standardized in carvedilol units, mg	10.0 (7.5-20.0)	10.0 (5.0-20.0)	0.029	0.91
ACEi or ARB	4356 (81.1)	3501 (75.1)	0.147	<0.001
MRA	1840 (34.3)	1670 (35.8)	0.032	0.11
Loop diuretics	3595 (69.4)	2945 (66.3)	0.065	0.001
Thiazides	158 (3.2)	174 (4.2)	0.050	0.017
Digitalis	1571 (30.3)	1185 (26.1)	0.094	<0.001
Amiodarone	587 (10.9)	513 (11.0)	0.002	0.91
Oral inotropes	220 (4.1)	249 (5.3)	0.059	0.003

ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, brain-type natriuretic peptide; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; LVDd, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; SBP, systolic blood pressure; SMD, standardized mean difference.

Table S2. The relationship between dose of beta-blocker and left ventricular remodeling.

Dataset	Outcome	No beta-blocker	Beta-blocker	
			<50% of target dose	≥50% of target dose
		n=1266	n=936	n=2729
prior LVEF< 40%	Reduction in LVEF ≥5%	1 [reference]	0.77 (0.61-0.97)	0.71 (0.59-0.87)
current LVEF ≥40%	Reduction in LVEF ≥10%	1 [reference]	0.74 (0.56-0.98)	0.73 (0.58-0.92)
	Reduction in LVEF ≥15%	1 [reference]	0.65 (0.45-0.94)	0.60 (0.45-0.80)
		n=811	n=677	n=1986
prior LVEF< 35%	Reduction in LVEF ≥5%	1 [reference]	0.73 (0.54-0.97)	0.65 (0.51-0.82)
current LVEF ≥40%	Reduction in LVEF ≥10%	1 [reference]	0.70 (0.50-0.98)	0.65 (0.49-0.86)
	Reduction in LVEF ≥15%	1 [reference]	0.66 (0.43-1.01)	0.55 (0.38-0.78)
		n=468	n=435	n=1312
prior LVEF< 30%	Reduction in LVEF ≥5%	1 [reference]	0.87 (0.60-1.25)	0.64 (0.47-0.87)
current LVEF ≥40%	Reduction in LVEF ≥10%	1 [reference]	0.74 (0.48-1.13)	0.61 (0.42-0.87)
	Reduction in LVEF ≥15%	1 [reference]	0.69 (0.41-1.15)	0.52 (0.33-0.80)
		n=499	n=358	n=1230
prior LVEF< 40%	Reduction in LVEF ≥5%	1 [reference]	0.66 (0.45-0.97)	0.61 (0.45-0.82)
current LVEF ≥50%	Reduction in LVEF ≥10%	1 [reference]	0.56 (0.36-0.87)	0.62 (0.44-0.87)
	Reduction in LVEF ≥15%	1 [reference]	0.51 (0.30-0.86)	0.54 (0.36-0.81)

Taking ≥50% of target dose of beta-blockers was consistently associated with prevention of left ventricular remodeling.

Figure S1. Absolute standardized mean difference with or without adjustment for

propensity score.
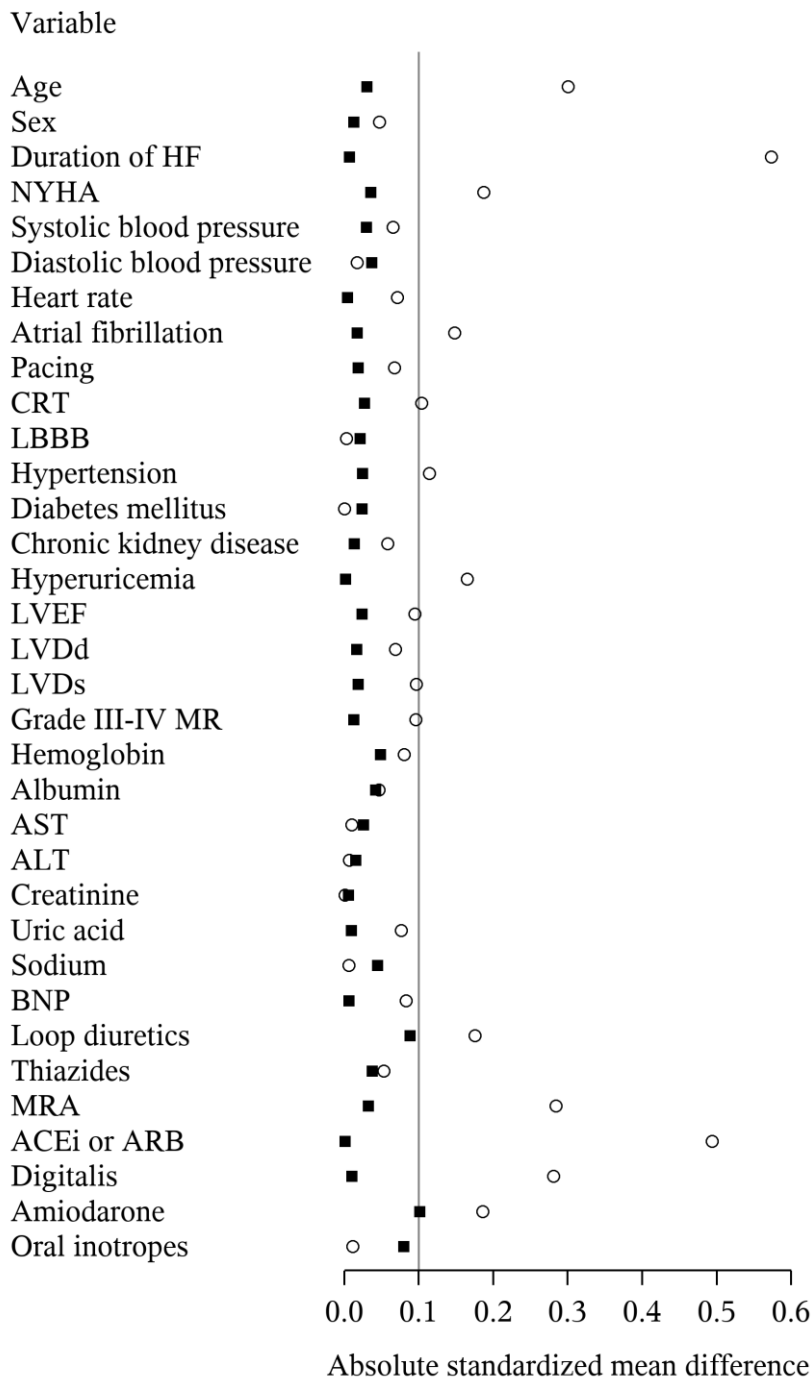
ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker;

BNP, brain-type natriuretic peptide; CRT, cardiac resynchronization therapy; HF, heart

failure; LBBB, left bundle branch block; MR, mitral regurgitation; MRA,

mineralocorticoid receptor antagonist; PS, propensity score.