

significantly improved after CRT device implantation in the responder group ( $0.47 \pm 0.07$  before vs  $0.50 \pm 0.07$  after,  $p = 0.04$ ), but DFT/RR did not in the nonresponder group ( $0.46 \pm 0.07$  before vs  $0.46 \pm 0.08$  after,  $p = \text{NS}$ ). Therefore, assessment of the overlap ratio of the E and A waves of transmitral flow may be more effective for evaluating AV dyssynchrony than DFT/RR.

Unexpectedly, the overlap ratio of the E and A waves was the only independent predictor of CRT response in our study, while the other conventional parameters were not. This may be explained by 3 mechanisms. First, overlap of the E and A waves of transmitral flow reflected electrical ventricular dyssynchrony.<sup>1</sup> An intraventricular conduction delay increases the pre-ejection interval of the left ventricle because of the delayed systole period. This causes abnormalities of diastolic function with shortening of the ventricular filling period by fusion of the E and A waves because the next E wave is delayed by an increase in the duration of the ventricular systole. In these patients, LV pacing may change the diastolic filling timing, using a timely atrial contraction more effectively. In the baseline characteristics of our study, left bundle branch block was more frequent in the higher overlap ratio group than in the lower overlap ratio group (64% vs 8%,  $p < 0.0001$ ). This evidence may support our speculation.

Second, the overlap ratio of the E and A waves is simple to measure. Mechanical dyssynchrony has been measured with conventional echocardiographic techniques, including M-mode, Doppler, and tissue Doppler imaging. However, no single echocardiographic measurement of dyssynchrony appears to have had a clinically relevant impact in large clinical trials.<sup>2,3</sup> Two-dimensional speckle-tracking imaging and real-time 3-dimensional echocardiography are promising methods to decrease nonresponse.<sup>12–17</sup> However, the reproducibility of these echocardiographic parameters remains controversial. Therefore, a simple and reproducible method is still desirable in clinical practice, and transmitral flow velocity is suitable for that purpose.

Third, our parameter does not require wall motion analysis. Echocardiography, in particular advanced quantitative techniques for regional wall motion that include tissue Doppler imaging, 2-dimensional speckle-tracking imaging, and real-time 3-dimensional echocardiography, may help understand the complexity of LV mechanics,<sup>12–17</sup> but in patients with severe heart failure, poor LV wall motion often hampers an accurate assessment of LV dyssynchrony.<sup>17</sup> In a subanalysis of patients with LVEFs  $< 30\%$  in our study, those with overlap ratios of the E and A waves of  $\geq 33\%$  still included significantly more CRT responders than those with ratios  $< 33\%$ . This result demonstrates the advantage of our parameter in patients with poor LV wall motion. In our study, no single echocardiographic parameter of mechanical dyssynchrony used in the large clinical trials<sup>2,3</sup> was a predictor of response to CRT. However, a combination of the overlap ratio of the E and A waves and the indexes of mechanical dyssynchrony, especially in borderline cases, may help in making a clinical decision.

Our study did have several limitations. First, the fusion of the E and A waves is dependent on heart rate. In this study, there was no difference in heart rate between the responder and nonresponder groups ( $74 \pm 15$  vs  $76 \pm 15$  beats/min,

$p = \text{NS}$ ), and the overlap ratio of the E and A waves was not correlated with heart rate before CRT device implantation ( $r = 0.34$ ). Therefore, at least in our study, the overlap ratio of the E and A waves was not affected by heart rate.

Second, the optimization of the AV and ventricular-ventricular intervals after CRT was not determined. Some cases were optimized by echocardiography and some by device algorithms. However, we used the same optimization program for all patients, using echocardiography or the device algorithm after CRT device implantation.

Third, this simple method was not available in the patients with atrial fibrillation, because the A waves of the transmitral flow were not evaluated in these patients.

Fourth, the total number of responders was smaller than expected (48%), compared with previous CRT clinical trials. This is because our retrospective study population included many patients with severe progressive LV dysfunction. LV end-systolic volume and left atrial volume before CRT device implantation were  $184 \pm 82$  and  $100 \pm 44$  ml, respectively, and end-stage inotrope-dependent heart failure was observed in 21% of the patients in our study.

Finally, this study was a retrospective study, and the sample size was relatively small. A prospective analysis in a large-scale study is desirable.

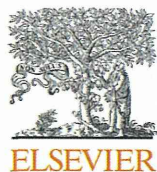
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## Disclosures

The authors have no conflicts of interest to disclose.

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## Original article

## Switching from carvedilol to bisoprolol ameliorates adverse effects in heart failure patients with dizziness or hypotension

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## ABSTRACT

**Background:** Treatment with carvedilol is an established primary therapy for patients with heart failure (HF). However, its most common adverse effects, dizziness and hypotension, often discourage continuation or dosage increase. The aim of this study was to examine whether switching to bisoprolol from carvedilol would help to avoid adverse symptoms and signs related to carvedilol administration.

**Methods and subjects:** Data were retrospectively collected from 23 patients with HF [age  $57 \pm 18$  years, left ventricular ejection fraction (LVEF)  $33 \pm 15\%$ ] who could not increase the dosage of carvedilol because of dizziness or hypotension, defined as systolic blood pressure  $<90$  mmHg. Before and immediately after, and 6 months after switching to bisoprolol, we examined symptoms, vital signs, laboratory data, and New York Heart Association functional class. Furthermore, left ventricular (LV) dimension and ejection fraction (EF) were evaluated in 19 patients using echocardiography.

**Results:** All 13 patients with dizziness (100%) and 9 of 16 with hypotension (56%) were relieved of adverse symptoms or signs. The mean dose of carvedilol before switching was  $5.60 \pm 3.43$  mg. Immediately after the switch, the mean dose of bisoprolol was  $1.84 \pm 1.08$  mg and then increased to  $3.13 \pm 1.74$  mg after 6 months ( $p < 0.01$ ). At 6-month follow-up examinations, LV function determined by LVEF was significantly improved, which was accompanied by increased exercise tolerance.

**Conclusion:** Switching from carvedilol to bisoprolol may help with continuation of  $\beta$ -blocker treatment as well as dosage increase in HF patients with adverse symptoms or signs, allowing them to reach the target dose.

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## Introduction

Heart failure (HF) is one of the most serious causes of morbidity and mortality in both developed and developing countries [1], while increased survival was recently demonstrated with continuation of  $\beta$ -blocker therapy in patients with chronic HF and reduced ejection fraction [2–4]. Of the various  $\beta$ -blockers given to affected patients, carvedilol is a multiple action non-selective  $\beta$ -adrenergic receptor blocker that also induces  $\alpha_1$ -adrenergic receptor blockade and has been shown to improve the state of HF patients in

a number of large-scale trials [5–7]. However, the most common adverse clinical effects of carvedilol are dizziness and hypotension [8], and some patients are not able to continue or up-titrate the drug because of these adverse symptoms/signs, which seem to be mainly related to an  $\alpha_1$  blockade effect (vasodilation). On the other hand, bisoprolol, a highly selective  $\beta_1$ -adrenergic receptor blocker, has also been shown to be effective for HF patients in several studies [9–11].

We speculated that switching from carvedilol to bisoprolol would be useful for avoiding adverse symptoms/signs, and lead to continuation or up-titration of  $\beta$ -blocker administration in HF patients who had adverse effects related to carvedilol administration. In the present study, we retrospectively examined changes in symptoms, blood pressure, heart rate, New York Heart Association (NYHA) functional class, laboratory data, and echocardiography parameters before and after switching to bisoprolol in patients who showed adverse effects due to carvedilol.

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## Methods

### Study patients

This retrospective study was conducted using data from a large university hospital. The protocol used complies with the Declaration of Helsinki and was approved by our Institutional Ethics Committee, which waived the need for patient consent because of the retrospective nature of the study. Between August 2005 and June 2011, we identified 1056 consecutive patients with left ventricular (LV) ejection fraction (EF) less than 50% who were receiving carvedilol in our hospital database. Among those, 23 in- and outpatients with chronic HF had switched medication because of persistent adverse effects of carvedilol, such as dizziness and hypotension with systolic blood pressure < 90 mmHg [12]. The diagnosis of heart failure was primarily based on signs and symptoms derived from a thorough history review and physical examination [1].

### Data collection and study design

Baseline demographic information was retrospectively collected from the medical records, including age, sex, height, weight, NYHA functional class, dose of carvedilol, duration of carvedilol therapy, underlying heart disease (ischemic or non-ischemic), comorbidities (e.g. atrial fibrillation, diabetes mellitus, chronic obstructive pulmonary disease), and medications (e.g. angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, calcium channel blocker, diuretic, mineralocorticoid receptor antagonist, digoxin, statin, pimobendan, aspirin, clopidogrel). The following assessments were performed: evaluation of adverse symptoms/signs, dose of  $\beta$ -blocker, laboratory data, B-type natriuretic peptide (BNP), echocardiographic parameters, NYHA functional class before the switch, and 6-month follow-up examination findings.

The effects of switching from carvedilol to bisoprolol on adverse symptoms/signs were evaluated immediately after the change or at the first follow-up visit, as well as at the 6-month follow-up examination. Improvement of dizziness was determined by subjective reports from the patient, and relief of hypotension was defined as a blood pressure increase of more than by 10 mmHg in 3 consecutive readings obtained before and after switching medications. To investigate the effects of the switch on cardiac reverse remodeling and symptoms, we also analyzed vital signs, echocardiographic and laboratory data, and NYHA functional class prior to and immediately after switching, and at the 6-month follow-up examination.

### Initiation of and switching from carvedilol to bisoprolol

Principally, we treat our patients using optimal medical therapy in line with the guidelines for management of chronic HF (<http://www.j-circ.or.jp/guideline/>). Treatment with carvedilol was initiated at low doses (1.25 or 2.5 mg/day), followed by gradual increments (usually every 1–2 weeks) if the lower dose was well tolerated, during which the patient was closely monitored for changes in vital signs and symptoms. Planned dosage increases of carvedilol should be delayed until side effects observed with lower doses have disappeared. Every effort to achieve the target dose of carvedilol (usually, 10 mg twice daily) was made by the attending physician [7]. After the appearance of adverse effects, the attending physician switched from carvedilol to bisoprolol and up-titrated the dose of bisoprolol to accomplish the target dose of 5 mg once daily. The tolerable maximum dosage of bisoprolol was determined by the physician after the switch.

### Echocardiography

Two-dimensional echo and Doppler recordings for each patient were obtained using a commercially available echocardiographic machine equipped with a 12-MHz transducer (Agilent Sonos 7500; Philips Medical Systems, Andover, MA, USA) at a standard clinical echocardiography laboratory. The investigators were blinded to the results of other tests and clinical examinations. LV end-diastolic dimension (LVDD) and end-systolic dimension (LVDs) were determined from 2-D transthoracic echocardiographic images using M-mode in parasternal long-axis views. LVEF was calculated using Simpson's biplane method with apical 2- and 4-chamber views [13].

### Statistical analyses

All continuous values are expressed as the mean  $\pm$  standard deviation, and data for categorical variables are expressed as the number and percentage of patients. All continuous variables were checked for normality using a Shapiro–Wilk test and normal probability plot. To assess the mean differences in continuous variables between before and after switching, and at the 6-month follow-up examination, we used a Student's paired *t*-test, while a Wilcoxon signed-rank test was performed to evaluate changes in non-normally distributed variables. The vital findings among the 3 different periods were tested using one-way analysis of variance (ANOVA) followed by a Tukey–Kramer multiple comparison test. Differences were considered significant at  $p < 0.05$ . All statistical analyses were performed using commercially available statistical software JMP 10.0 (SAS Institute, Cary, NC, USA).

## Results

### Patient characteristics

Characteristics of the 23 patients are shown in Table 1. The average age was 57 years and 74% were male. The majority of patients had NYHA class III or IV heart failure symptoms, while 10 (43%) had advanced systolic HF (LVEF < 30%). Nine patients (39%) had atrial fibrillation, 5 diabetes mellitus, and 1 chronic obstructive pulmonary disease (COPD) without bronchial asthma. There was no patient receiving both angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in a concomitant manner. Fourteen patients were treated with enalapril (mean dose  $2.68 \pm 1.19$  mg), 2 were taking candesartan (2 mg), and 1 was taking telmisartan (20 mg).

### Adverse effects of carvedilol administration

None of the 23 patients was able to up-titrate carvedilol to the target dose of 20 mg because of adverse events. The reasons for switching from carvedilol to bisoprolol were dizziness in 13 patients and hypotension in 16; 6 were accompanied by dizziness but 10 were not. The dizziness disappeared in all 13 patients after switching, while hypotension improved in 9 of 16. Moreover, there were no new reports of dizziness or hypotension associated with bisoprolol use during the study period (Fig. 1).

### Switching from carvedilol to bisoprolol

The median duration of carvedilol administration before switching was 128 days (interquartile range, 23–707 days) (Table 1). The daily dose of carvedilol before switching was  $5.60 \pm 3.43$  mg. Immediately after the switch, the initial dose of bisoprolol was

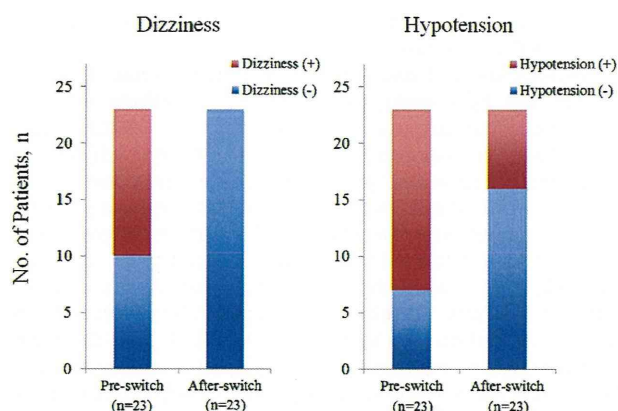
**Table 1**  
Patient characteristics.

Variable	n = 23
Age, (years)	57 ± 18
Male, n (%)	17 (74)
Body weight (kg)	56 ± 11
Body surface area (m <sup>2</sup> )	1.56 ± 0.16
Body mass index (kg/m <sup>2</sup> )	20.2 ± 3.2
New York Heart Association class, n (%)	
II	11 (48)
III	10 (43)
IV	2 (9)
Duration of carvedilol therapy (days)	
Median	128
Interquartile range	23–707
Daily dose of carvedilol, n (%)	
<5.0 mg	8
5.0–7.4 mg	8
7.5–10.0 mg	7
>10.0 mg	0
Etiology, n (%)	
Ischemic cardiomyopathy	7 (30)
Non-ischemic (systolic failure)	16 (70)
Comorbidity, n (%)	
Atrial fibrillation, n (%)	9 (39)
Diabetes mellitus, n (%)	5 (22)
COPD, n (%)	1 (4)
Medication at baseline, n (%)	
ACE inhibitor (Enalapril), n (%)	14 (61)
Angiotensin receptor blocker, n (%)	3 (13)
Calcium channel blocker, n (%)	2 (9)
Diuretic, n (%)	17 (74)
Mineralocorticoid receptor antagonist, n (%)	17 (74)
Digoxin, n (%)	6 (23)
Statin, n (%)	4 (17)
Pimobendan, n (%)	6 (23)
Aspirin, n (%)	9 (39)
Clopidogrel, n (%)	3 (13)
Adverse symptoms/signs, n (%)	
Dizziness, n (%)	13 (57)
Hypotension (<90 mm Hg), n (%)	16 (70)
Vital signs	
Blood pressure (mmHg)	
Systolic	96 ± 19
Diastolic	58 ± 7
Heart rate (beats/min)	76 ± 11
Echocardiographic parameters	
LV end-diastolic dimension (mm)	60.1 ± 12.9
LV end-systolic dimension (mm)	51.1 ± 15.6
LV ejection fraction (%)	32.7 ± 14.8
B-type natriuretic peptide (pg/ml)	
Median	245
Interquartile range	111–460
Laboratory parameters	
Hemoglobin (g/dl)	11.7 ± 1.8
Blood urea nitrogen (mg/dl)	23.5 ± 10.5
Serum creatinine (mg/dl)	1.11 ± 0.43
eGFR (ml/min)	59.1 ± 23.4
Serum sodium (mEq/l)	136.2 ± 3.7
Serum potassium (mEq/l)	4.3 ± 0.4

Data given as mean ± SD or the number (percentage).

COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme; LV, left ventricular; eGFR, estimated glomerular filtration rate

1.84 ± 1.08 mg and then increased to 3.13 ± 1.74 mg after 6 months ( $p < 0.01$ ). Notably, the dose of bisoprolol reached the target dose in 9 of 23 patients (39%) at 6 months. Bisoprolol was continued in all of the patients and not replaced with another  $\beta$ -blocker during the study period.

**Fig. 1.** Changes in dizziness and hypotension at pre-switch, and after-switch.

#### Changes in vital findings, and echocardiographic and laboratory parameters after switching

Of the 23 studied patients, only 19 provided complete echocardiographic and laboratory data at 6 months after switching. Data for 4 who underwent 6-month follow-up examinations at the referring hospital were not included in this analysis.

There was a significant increase in both systolic and diastolic blood pressure from before the switch to 6 months after, whereas heart rate showed no significant difference and plasma BNP concentration was not significantly improved (Table 2). Blood pressure changed from 94.4 ± 18.7 mmHg at baseline to 99.1 ± 17.0 mmHg immediately after switching ( $p = \text{NS}$ ) and increased to 110.3 ± 21.2 mmHg at 6 months ( $p < 0.05$ ). In the 11 patients with dizziness, blood pressure changed from 101 ± 22 to 103 ± 20 mmHg ( $p = \text{NS}$ ) from baseline to immediately after switch, while that change was from 85 ± 3 to 92 ± 8 mmHg ( $p = 0.007$ ) in the 14 with hypotension.

LVDD did not significantly change and LVDs was significantly decreased at 6 months after switching. As a consequence, LVEF showed a significant improvement, suggesting that significant LV reverse remodeling had occurred.

Plasma BNP concentration was not significantly improved, suggesting that no significant changes in cardiac wall stress occurred after switching. As for laboratory parameters, renal function, determined by serum creatinine level and estimated glomerular filtration rate, was slightly decreased after switching.

#### Exercise tolerance

NYHA functional class was significantly improved from before to 6 months after switching, as the proportion of patients rated as NYHA class I (no symptoms) or II heart failure increased, and that of those with class III or IV heart failure decreased during the interval from baseline to the 6-month follow-up visit (Fig. 2).

#### Discussion

Our results demonstrated that switching to bisoprolol from carvedilol is useful for avoiding adverse symptoms/signs, and can lead to continuation or up-titration of  $\beta$ -blocker administration in HF patients experiencing adverse effects related to carvedilol. The major findings of the present study were (1) all patients with dizziness could be relieved from that adverse symptom and hypotension was improved in more than half after switching to bisoprolol, and (2) at 6 months after switching from carvedilol to bisoprolol, the majority of patients showed significant reverse LV remodeling

and improvement in symptoms, while no significant reduction in plasma BNP level occurred.

Previous US trial data have shown that dizziness accounts for 33% and hypotension 9% of all adverse effects related to carvedilol administration [5]. In addition, the GESICA registry states that hypotension is the main reason for not achieving the target dose of carvedilol [14]. One possible explanation for the favorable result of switching could be differences in  $\alpha$ 1-blocking effect. In a previous review article, dizziness and hypotension were attributed to relaxation of blood vessels induced by  $\alpha$ 1 adrenoceptor blockade [15], while the same investigator also demonstrated that dizziness was not related to changes in blood pressure, but rather to central nervous system effects [16]. Of note, there were 6 patients with dizziness regardless of the absence of hypotension. Since autonomic nervous system dysfunction was not assessed, we were unable to definitively diagnose any of the present patients with autonomic dysregulation, such as orthostatic hypotension. Nevertheless, our results suggest that switching from carvedilol to bisoprolol is a practical and safe method for clinically stable patients with LV dysfunction.

In addition, we found that the dose of bisoprolol was significantly increased at 6 months after switching, which was accompanied by disappearance of carvedilol-related side-effects. Given that the equivalent dose of bisoprolol is 1/5 that of carvedilol, as shown in some large trials [12,17], the mean dose of carvedilol (5.60 mg) at pre-switch was equivalent to 1.12 mg of bisoprolol. The patients were switched to bisoprolol at 1.84 mg and the dose was finally increased to 3.13 mg during the study period, thus the bisoprolol dosage after 6 months was significantly increased. Based on our findings, we consider that switching from carvedilol to bisoprolol may also help with up-titration of the  $\beta$ -adrenergic receptor blocker agent in such settings.

Several studies have shown that the mortality benefits of carvedilol and other  $\beta$ -blockers are dose dependent [7,18,19]. Also, major society guidelines recommend that every effort be given to achieve the target dose of administered  $\beta$ -blockers [1,20], although the dose-dependent benefits remain controversial [21]. It is also important to exercise caution in Japan where the recommended

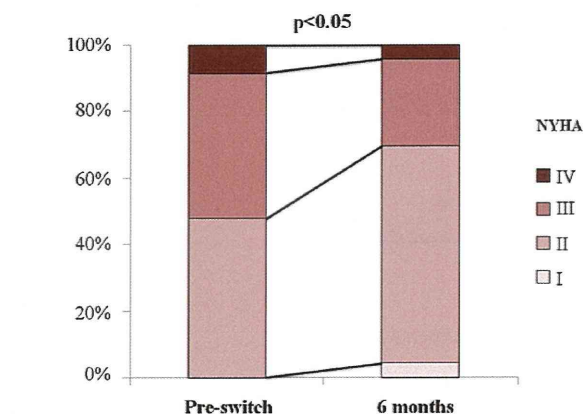


Fig. 2. Effects of switching from carvedilol to bisoprolol on New York Heart Association (NYHA) functional class.

maximum doses of  $\beta$ -blockers are less than half of those in Western countries, while there is limited evidence of the tolerability of daily carvedilol doses higher than 20 mg in Japanese chronic HF patients. In our study, LVEF and NYHA functional class were significantly improved after switching from carvedilol to bisoprolol. It is well known that  $\beta$ -blocker administration reduces LV volume along with improvement in systolic function, leading to improvement in prognosis [22], which also occurs in a dose-dependent manner [7]. Therefore, switching from carvedilol to bisoprolol may provide beneficial effects in regard to prognosis and/or reverse remodeling in patients who experience difficulty with continuation or up-titration of carvedilol because of adverse effects such as dizziness or hypotension.

Despite LV reverse remodeling and improvement in NYHA class, there was no significant change in BNP level. BNP is a hormone of cardiac origin that is secreted specifically from the ventricle in response to volume expansion and pressure overload [23], as well as abnormal constructive change such as hypertrophy and/or fibrosis. Our data suggest that the improvements in functional class and

Table 2

Vital signs, laboratory data, and echocardiographic parameters.

Variables	Pre-switch n = 19	After-switch n = 19	6 months n = 19	P-Value
<b>Vital signs</b>				
Blood pressure (mmHg)				
Systolic	94.4 ± 18.7	99.1 ± 17.0	110.3 ± 21.2 <sup>†</sup>	<0.05 <sup>†</sup>
Diastolic	58.6 ± 5.5	55.6 ± 7.8	63.5 ± 10.3 <sup>‡</sup>	<0.05 <sup>†</sup>
Heart rate (beats/min)	76 ± 12	74 ± 13	74 ± 12	NS
<b>Echocardiographic parameters, n (%)</b>				
LV end-diastolic dimension (mm)	61.1 ± 13.7	n.a.	59.3 ± 14.4	NS
LV end-systolic dimension (mm)	52.6 ± 15.8	n.a.	47.6 ± 16.8	p < 0.01
LV ejection fraction (%)	30.7 ± 13.5	n.a.	39.9 ± 13.8	p < 0.001
<b>B-type natriuretic peptide (pg/ml)</b>				
Median	223	n.a.	194	NS <sup>*</sup>
Interquartile range	114–458	n.a.	86–331	
<b>Laboratory parameters, n (%)</b>				
Hemoglobin (g/dl)	11.6 ± 1.8	n.a.	12.0 ± 1.6	NS
Blood urea nitrogen (mg/dl)	23.8 ± 8.7	n.a.	27.2 ± 11.6	p = 0.054
Serum creatinine (mg/dl)	1.1 ± 0.5	n.a.	1.2 ± 0.5	<0.01
eGFR (mL/min per 1.73 m <sup>2</sup> )	59.9 ± 25.4	n.a.	53.9 ± 18.5	<0.05
Serum sodium (mEq/l)	137 ± 3	n.a.	138 ± 4	NS
Serum potassium (mEq/l)	4.3 ± 0.5	n.a.	4.5 ± 0.4	NS

Data given as mean ± SD or the number (percentage).

LV, left ventricular; eGFR, estimated glomerular filtration rate.

\* Tested with Wilcoxon signed-rank method.

† Tested with one-way analysis of variant (ANOVA).

‡ >Pre-switch, Tukey–Kramer test P < 0.05.

§ >After-switch, Tukey–Kramer test P < 0.05.

LV reverse remodeling after switching may be mainly mediated by neurohormonal modulations of the adrenergic receptor blockers themselves, rather than by a reduction in circulating plasma/blood volume and subsequent decreased wall stress, or decreased pressure overload.

Although a favorable effect of switching to bisoprolol was shown in patients with adverse effects due to carvedilol administration in our study, there were two unexpected results. First, heart rate was not significantly changed, although there was improvement in blood pressure after switching to and increasing the dose of bisoprolol, which might have been due to the highly selected population with hypotension in our study. It is also conceivable that our study patients had already taken carvedilol before switching, thus no heart rate reduction could be achieved with an increase in dose. Second, there was significant exacerbation of renal function found in the present subjects, which was recently reported to be a strong predictor of prognosis in patients with HF [24]. It is also well known that renal function is progressively worsened in HF patients. Konishi et al. reported that there was no difference regarding impact on renal function between carvedilol and bisoprolol [25], while worsening renal function was attributed to use of diuretics in that study. On the other hand, it has been reported to be important whether the pharmacological intervention improves clinical outcomes even in such HF patients [26]. As there was no control group without  $\beta$ -blocker administration in the present study, we cannot conclude whether the change in estimated glomerular filtration rate during 6 months could be attributed to the switch of carvedilol to bisoprolol, other drugs (diuretics, etc.), or the natural course of HF. Additional well-designed prospective large-scale investigations are needed to more closely examine the efficacy of this switching strategy.

### Study limitations

The main limitations of the present study are the small number of enrolled patients and absence of a control group. Moreover, although clinical data obtained at 6 months after switching are considered to be integral to understand the immediate effect of the  $\beta$ -blocker itself and LV reverse remodeling, we were unable to assess laboratory and echocardiographic data immediately after the switch. Therefore, it is not possible to definitively conclude from our findings that switching from carvedilol to bisoprolol will produce favorable effects in patients with chronic HF in all settings. It is well known that systolic blood pressure increases later in HF patients with hypotension who respond to  $\beta$ -blockers [27], thus the clinical implications of our observations are also limited. Nevertheless, our retrospective series consisted of consecutive patients with impediments caused by carvedilol administration in actual clinical settings, thus the results may provide helpful insight for determining effective  $\beta$ -blockade strategies for HF patients.

### Conclusion

Switching from carvedilol to bisoprolol may help with continuation of  $\beta$ -blocker treatment as well as dosage increase in patients with adverse symptoms or signs, allowing them to reach the target dose.

### Disclosures

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