Differential Response to Heart Rate Reduction by Carvedilol in Heart Failure and Reduced Ejection Fraction Between Sinus Rhythm and Atrial Fibrillation

— Insight From J-CHF Study —

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Background: Heart rate (HR) reduction by β-blocker might not benefit patients with heart failure and reduced ejection fraction (HFrEF) with atrial fibrillation (AF).

Methods and Results: The J-CHF study was a prospective randomized multicenter trial that assigned 360 HFrEF patients to a 2.5 mg/5 mg/20 mg target dose of carvedilol. Carvedilol was uptitrated over 8 weeks and then the dose was fixed. Of 321 patients available for analysis, AF was identified in 65 (20%). Using the median absolute change in HR at 32 weeks (ΔHR), the subjects were further divided into group A (ΔHR >−6 beats/min) and B (ΔHR ≤−6 beats/min). Both in sinus rhythm (SR) and AF, baseline characteristics and achieved carvedilol dose were similar between groups A and B. In SR, the time-dependent change in left ventricular EF (LVEF) and LV end-diastolic dimension (LVEDD) over 56 weeks was more favorable in B compared with A (ΔLVEF, P=0.036; ΔLVEDD, P=0.047), and ΔHR was independently associated with ΔLVEF (P=0.040). Group B had a lower rate of the primary endpoint, defined as a composite of death and hospitalization due to cardiovascular causes including acute decompensated HF at 3 years (P=0.002). ΔHR was an independent predictor of the primary endpoint (P=0.01), but this was not observed in AF.

Conclusions: Response to the carvedilol HR reduction might differ in HFrEF between SR and AF.

Key Words: Atrial fibrillation; Carvedilol; Heart failure with reduced ejection fraction

In patients with heart failure and reduced ejection fraction (HFrEF), a higher resting heart rate (HR) is associated with higher morbidity and mortality.[1–3] Beta-blockers have been recommended for all patients with HFrEF to reduce morbidity and mortality unless contra-indicated.[4] The clinical benefit of β-blockers has been shown to be mainly attributed to HR reduction.[5,6] Atrial fibrillation (AF) is the common morbidity of HF.[7] The prevalence of AF in HF has been increasing and its presence has substantial influence on clinical course and outcome.[7–9] Some recent studies have raised doubts about the beneficial effect of β-blockers, or of HR reduction by β-blockers, on clinical outcome in HFrEF concomitant with AF. In the CIBIS II and MERIT-HF studies, there was no mortality benefit of the β-blockers bisoprolol or metoprolol succinate compared with placebo in patients with HFrEF with AF.[10,11] In a meta-analysis β-blockers were associated with a mortality reduction in HFrEF patients with SR but not in those with AF.[12] Subsequently, an association between lower HR and more favorable survival was not observed in HFrEF with AF.[13,14]

The Japanese Chronic Heart Failure (J-CHF) study was a prospective randomized study to determine the optimal dose of carvedilol by comparing the efficacy and safety of 3 different doses of carvedilol, and the best predictors of effective outcomes in Japanese patients with HFrEF.[15–17] In this substudy, we investigated whether the benefit of HR reduction by carvedilol differs between HFrEF patients with sinus rhythm (SR) and those with AF in terms of left ventricular (LV) reverse remodeling and subsequent

Figure 1. Study flowchart. AF, atrial fibrillation; HR, heart rate; pts, patients; SR, sinus rhythm. Data given as median (IQR) or n (%).

clinical outcomes.

Methods

Subjects

The J-CHF study was conducted as a prospective, randomized, multicenter trial that enrolled Japanese stable HFrEF patients.[15] The J-CHF study was approved by the Ethics Committee of Hokkaido University Graduate School of Medicine, Hokkaido, Japan, and complies with the Declaration of Helsinki. The institutional review board of each participating institution approved the J-CHF study protocol. The patients had stable CHF (New York Heart Association [NYHA] class II/III) with reduced EF (LVEF ≤40%), were not currently taking carvedilol, were between 20 and 80 years of age, and could be inpatients or outpatients. Key exclusion criteria were cardiogenic shock, systolic blood pressure (SBP) <80 mmHg, severe arrhythmia (e.g., sustained ventricular tachycardia, ventricular fibrillation), bradycardia (<50 beats/min), second degree or advanced atrioventricular block, recent myocardial infarction, coronary artery bypass graft or percutaneous coronary intervention. This study was originally designed to clarify the optimal dose of carvedilol and the subjects were randomly assigned to 2.5 mg/5 mg/20 mg carvedilol groups according to the target dose. Between July 2003 and January 2008, 364 patients were registered. Using centralized computer-generated randomization with an algorithm based on the underlying disease, severity, age, and sex, the 364 patients were randomly allocated using a 1:1:1 ratio to 1 of 3 carvedilol groups (2.5 mg, 5 mg, or 20 mg daily). Other β-blockers were prohibited, as were α-blockers, αβ-blockers, and inotropic agents other than digitalis.

A total of 237 clinical institutes all over Japan took part

in this study, and the subjects were enrolled in these institutes (**Supplementary Appendices 1,2**). Carvedilol was introduced for all patients and uptitrated to each target dose over 8 weeks. In this substudy, the patients were divided into the 2 groups SR and AF based on electrocardiogram (ECG) at baseline (**Figure 1**). For each of the SR and AF groups, the patients were further divided into 2 groups according to the median (−6 beats/min) absolute change in HR (ΔHR) at 32 weeks after carvedilol introduction. Reverse remodeling and survival after clinical events were compared between group A (ΔHR >−6 beats/min) and group B (ΔHR ≤−6 beats/min).

Study Design

The design of the J-CHF study is outlined in **Supplementary Figure 1**. Following an 8-week observation period, carvedilol was titrated upward over 8 weeks ("uptitration period") from 1.25 mg twice daily to the target dose of 10 mg twice daily based on tolerability. Thereafter, patients were seen every 2–8 weeks for the 3-year follow-up. At weeks 8, 32, and 56, patients were evaluated for NYHA class. In addition, ECG, chest X-ray, echocardiogram, and laboratory tests including plasma B-type natriuretic peptide (BNP) were also conducted ("fixed dose maintenance period"). LVEF was measured using the modified Simpson method on echocardiography or using radionuclide ventriculography. The primary endpoint was the composite of all-cause mortality and hospitalization due to cardiovascular (CV) causes including acute decompensated HF (ADHF).[15]
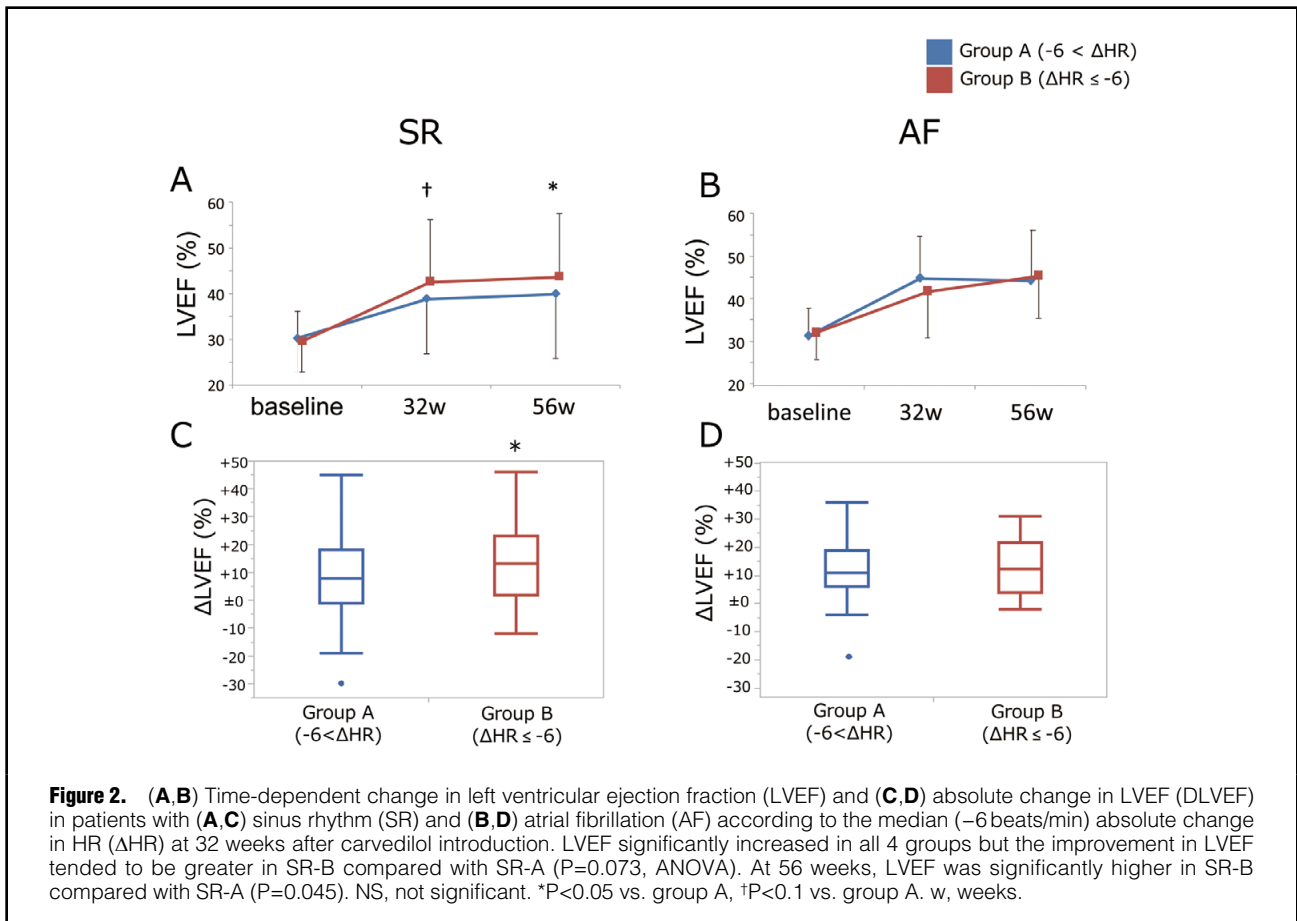
Statistical Analysis

Data are expressed as mean±SD for normally distributed data and median (IQR) for non-normally distributed data. Differences between groups were compared using the

Table 1. HFrEF Patient Baseline Characteristics vs. ΔHR						
	SR			AF		
	Group A (ΔHR >−6 beats/min) (n=116)	Group B (ΔHR ≤−6 beats/min) (n=140)	P-value	Group A (ΔHR >−6 beats/min) (n=30)	Group B (ΔHR ≤−6 beats/min) (n=35)	P-value
Age (years)	61 (53–70)	61 (53–70)	0.84	64 (59–71)	61 (50–69)	0.16
Gender (male)	81 (70)	95 (68)	0.73	26 (87)	32 (91)	0.54
BMI (kg/m^2)	22.2 (20.5–25.1)	23.5 (20.6–26.4)	0.11	23.3 (20.7–26.3)	23.5 (22.0–25.6)	0.66
Ischemic etiology	37 (32)	31 (22)	0.08	7 (23)	3 (9)	0.10
NYHA (II/III)	101/15 (87/13)	110/30 (79/21)	0.07	27/3 (90/10)	29/6 (83/17)	0.40
Comorbidities						
CVD	6 (5)	5 (4)	0.14	2 (7)	3 (9)	0.81
HT	47 (41)	60 (43)	0.71	14 (47)	12 (34)	0.31
HL	47 (41)	62 (44)	0.54	8 (27)	12 (34)	0.51
DM	37 (32)	31 (22)	0.08	8 (27)	5 (14)	0.21
Lab data						
Hb (g/dL)	14.1 (13.0–14.9)	13.9 (12.4–15.4)	0.63	14.9 (13.5–16.3)	15.6 (14.6–16.4)	0.17
BNP (pg/mL)	244 (116–423)	211 (88–470)	0.34	251 (121–536)	237.0 (141–727)	0.55
Cr (mg/dL)	0.9 (0.7–1.0)	0.9 (0.7–1.1)	0.45	0.9 (0.8–1.0)	1.0 (0.8–1.2)	0.38
eGFR (mL/min/1.73 m^2)	64.8 (53.9–79.6)	64.0 (49.8–76.4)	0.33	63.2 (55.6–72.3)	61.1 (50.6–75.3)	0.83
Na (mEq/L)	140 (139–142)	141 (139–142)	0.26	140 (139–142)	141 (139–143)	0.40
K (mEq/L)	4.3 (4.0–4.5)	4.3 (4.0–4.6)	0.81	4.3 (4.0–4.4)	4.1 (3.9–4.5)	0.55
FBG (mg/dL)	99 (90–112)	102 (93–112)	0.16	101 (90–116)	103 (89–115)	0.85
Echocardiography						
LVEF (%)	31.3 (25.3–36.5)	29.2 (25.0–35.0)	0.23	32.5 (27.5–37.7)	34.0 (28.0–37.3)	0.69
LVEDD (mm)	63 (58–70)	63 (58–68)	0.60	61 (57–67)	58 (55–60)	0.10
LVESD (mm)	54 (47–60)	54 (48–59)	0.91	50 (45–54)	48 (46–53)	0.51
LAD (mm)	41±8	42±7	0.16	45±7	50±8	0.02
Medication/Device						
ACEI	44 (38)	56 (40)	0.74	12 (40)	8 (23)	0.14
ARB	65 (56)	74 (53)	0.61	15 (50)	16 (46)	0.73
Ca blocker	11 (9)	26 (19)	0.04	9 (30)	3 (9)	0.02
Digitalis	20 (17)	21 (15)	0.63	18 (60)	27 (77)	0.14
Diuretics	88 (76)	108 (77)	0.81	24 (80)	24 (69)	0.29
Warfarin	24 (21)	37 (26)	0.54	21 (70)	34 (97)	0.001
Pacemaker	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
ICD	0 (0)	3 (2)	0.06	0 (0)	0 (0)	NA
Randomization and achieved dose						
Randomization (2.5 mg/5 mg/20 mg)	42/40/34 (36/34/29)	39/49/52 (28/35/37)	0.28	12/9/9 (40/30/30)	12/7/16 (34/20/46)	0.40
Final dose (mg)	5 (2.5–10)	5 (2.5–20)	0.08	5 (2.5–12.5)	5 (2.5–20)	0.47
Final dose/kg BW	0.08 (0.05–0.19)	0.09 (0.05–0.26)	0.18	0.07 (0.03–0.22)	0.09 (0.04–0.28)	0.51

Data given as n (%), mean±SD or median (IQR). ΔHR, absolute change in HR at 32 weeks; ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; BW, body weight; Ca blocker, calcium channel blocker; Cr, serum creatinine; CVD, cerebrovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; Hb, hemoglobin; HFrEF, heart failure with reduced ejection fraction; HL, hyperlipidemia; HR, heart rate; HT, hypertension; ICD, implantable cardioverter defibrillator; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; NA, not applicable; NYHA, New York Heart Association; SBP, systolic blood pressure; SR, sinus rhythm.

non-paired t-test or Mann-Whitney U rank-sum test for unpaired data as appropriate, and the chi-squared test for discrete variables. Repeated measures analysis of variance (ANOVA) was used to determine the difference in the time-related changes in LVEF, LV end-diastolic dimension (LVEDD), LV end-systolic dimension (LVESD) and BNP between group A and B for SR and AF. Multiple linear regression analysis was performed to estimate the independent determinants of absolute change in LVEF over 56 weeks for SR and AF, respectively. The variables of age,

sex, ischemic etiology, achieved dose of carvedilol, and ΔHR were included in the model. Kaplan-Meier survival curves for the primary endpoint according to median ΔHR status (group A and B) were analyzed using log-rank test for the SR and the AF groups. Cox proportional hazard model analysis was conducted to determine the independent predictors of the primary endpoint using independent variables such as age, sex, NYHA functional class, ischemic etiology, achieved dose of carvedilol and ΔHR. P<0.05 was considered statistically significant. Statistical analyses were

Figure 2. (**A,B**) Time-dependent change in left ventricular ejection fraction (LVEF) and (**C,D**) absolute change in LVEF (DLVEF) in patients with (**A,C**) sinus rhythm (SR) and (**B,D**) atrial fibrillation (AF) according to the median (−6 beats/min) absolute change in HR (ΔHR) at 32 weeks after carvedilol introduction. LVEF significantly increased in all 4 groups but the improvement in LVEF tended to be greater in SR-B compared with SR-A (P=0.073, ANOVA). At 56 weeks, LVEF was significantly higher in SR-B compared with SR-A (P=0.045). NS, not significant. *P<0.05 vs. group A, †P<0.1 vs. group A. w, weeks.

performed using JMP version 13.2.1 (SAS Institute, Cary, NC, USA).

Results

The subjects were randomly and equally allocated to 3 groups according to target dose (**Supplementary Figure 1**). On baseline ECG, AF was identified in 73 patients (20%), and the remaining 287 had SR (**Figure 1**). ΔHR was not available in 31 patients with SR, or in 8 patients with AF, resulting in a final group of 321 patients (SR, n=256; AF, n=65) available for analysis. After 32 weeks, median HR was reduced from 78 beats/min (IQR, 70–88 beats/min) to 72 beats/min (IQR, 66–84 beats/min) in the SR group, and from 80 beats/min (IQR, 68–90 beats/min) to 72 beats/min (IQR, 64–80 beats/min) in the AF group (P=0.46 between SR and AF by ANOVA). Baseline characteristics of group A (ΔHR >−6 beats/min) and group B (ΔHR ≤−6 beats/min) according to SR and AF status are listed in **Table 1**. There were no significant differences in the other baseline characteristics including baseline LVEF or final dose of carvedilol (**Table 1**).

Time-dependent changes in HR and SBP are listed in **Supplementary Table**. In the SR and AF groups, group B had a higher median HR at baseline but conversely a lower median HR at 32 weeks. During 56 weeks from baseline, LVEF significantly increased in all 4 groups (all P<0.001, **Figure 2A**). However, the improvement in LVEF tended to be greater in SR-B than in SR-A (P=0.073, ANOVA;

Figure 2A). At 56 weeks, LVEF was significantly higher in SR-B compared with SR-A (**Figure 2A**). Absolute change in LVEF (ΔLVEF) was significantly higher in SR-B than in SR-A (**Figure 2C**), but there was no significant difference between the AF groups (**Figure 2D**).

LVEDD significantly decreased during 56 weeks from baseline in all 4 groups (all P<0.001, **Figure 3A,B**). LVEDD was significantly smaller in SR-B compared with SR-A at 32 weeks and at 56 weeks (**Figure 3A**), but there was no significant difference between the AF groups either at 32 weeks or at 56 weeks (**Figure 3B**). ΔLVEDD tended to be greater in SR-B than in SR-A (**Figure 3C**) but there was no significant difference between the AF groups (**Figure 3D**). Similarly, LVESD significantly decreased during 56 weeks from baseline in all groups (all P<0.001, **Figure 4A,B**). LVESD was significantly smaller in SR-B compared with SR-A at 32 weeks and at 56 weeks (**Figure 4A**), but there was no significant difference between the AF groups at either of the time points (**Figure 4B**). ΔLVESD was significantly greater in SR-B compared with SR-A (**Figure 4C**) but there was no significant difference between the AF groups (**Figure 4D**). Log BNP significantly decreased in all 4 groups over 56 weeks (**Supplementary Figure 2**). At 56 weeks, log BNP tended to be lower in SR-B compared with SR-A (P=0.097), but there was no difference between the AF groups. Such a trend, namely, the more favorable LV reverse remodeling in SR-B than SR-A but no significant difference between AF-B and AF-A, was not observed when the subjects were divided according to median achieved
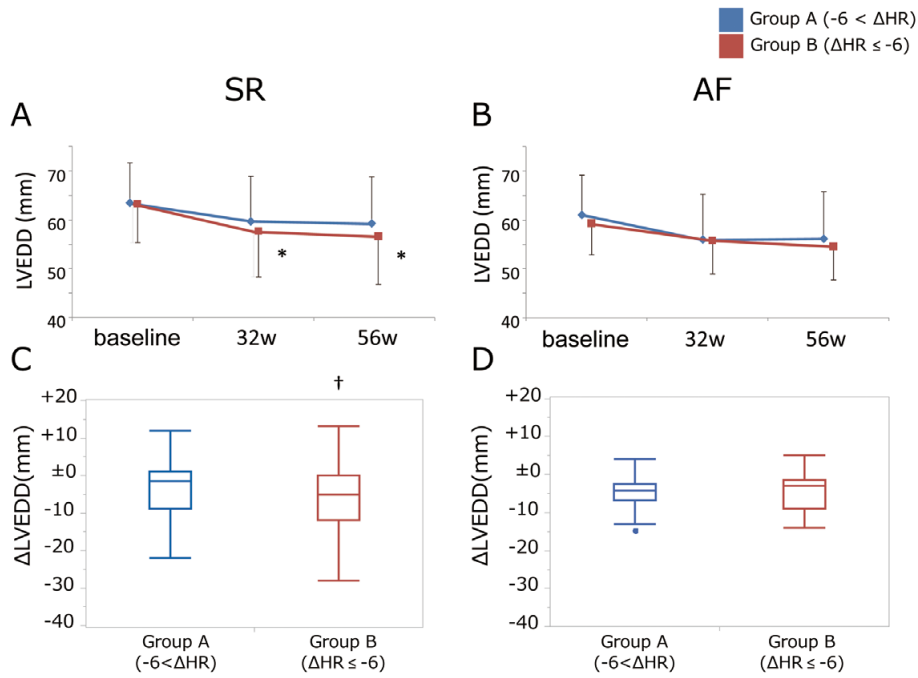
Figure 3. (**A**,**B**) Time-dependent changes in left ventricular end-diastolic diameter (LVEDD) and (**C**,**D**) absolute change in LVEDD (DLVEDD) in patients with (**A**,**C**) sinus rhythm (SR) and (**B**,**D**) atrial fibrillation (AF) according to the median (−6 beats/min) absolute change in HR (ΔHR) at 32 weeks after carvedilol introduction. LVEDD significantly decreased in all groups. At 32 weeks and 56 weeks, LVEDD was significantly smaller in SR-B than SR-A (32 weeks, P=0.048; 56 weeks, P=0.029). *P<0.05 vs. group A; †P<0.1 vs. group A. w, weeks.
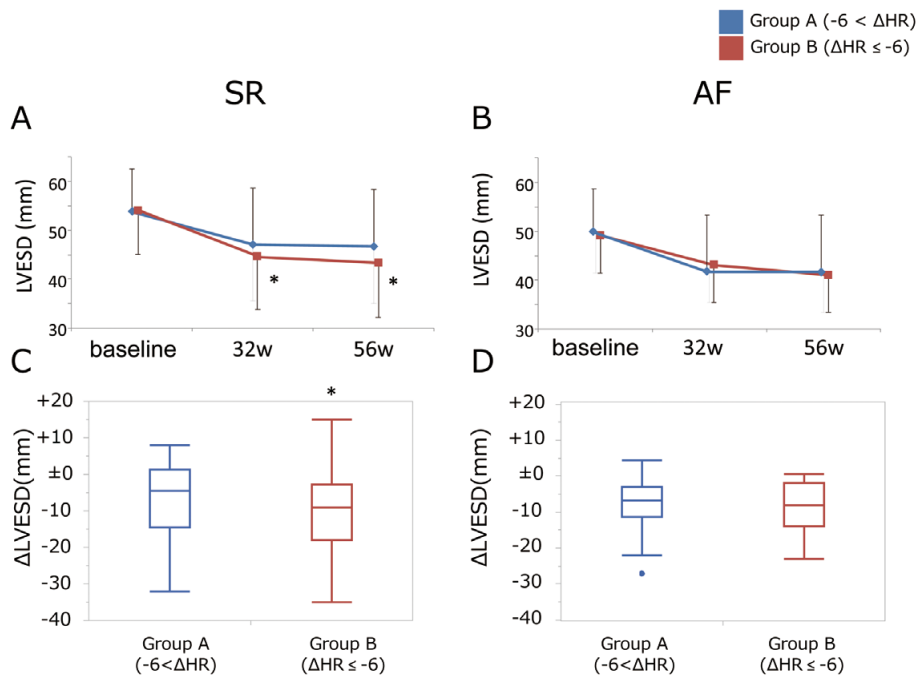

Figure 4. (**A**,**B**) Time-dependent changes in left ventricular end-systolic diameter (LVESD) and (**C**,**D**) absolute change in LVESD (DLVESD) in patients with (**A**,**C**) sinus rhythm (SR) and (**B**,**D**) atrial fibrillation (AF) according to the median (−6 beats/min) absolute change in HR (ΔHR) at 32 weeks after carvedilol introduction. LVESD significantly decreased in all groups. At 32 weeks and 56 weeks, LVESD was significantly smaller in SR-B than (32 weeks, P=0.049; 56 weeks, P=0.026). *P<0.05 vs. group A. w, weeks.

Table 2. Multivariate Indicators of ΔLVEF Over 56 Weeks in HFrEF Patients

	SR				AF			
	β	SEM	t-value	P-value	β	SEM	t-value	P-value
Age	−0.17	0.08	−2.47	0.014	−0.13	0.17	−0.80	0.43
Sex	0.15	2.09	2.26	0.025	−0.15	6.37	−0.98	0.33
CAD	−0.13	1.16	−1.84	0.067	−0.16	2.41	−0.99	0.33
Final dose of carvedilol	0.10	0.14	1.51	0.13	−0.14	0.22	−0.90	0.37
ΔHR	−0.14	0.06	−2.06	0.040	0.09	0.12	0.61	0.55

ΔHR, absolute change in HR; ΔLVEF, absolute change in LVEF; CAD, coronary artery disease; SEM, standard error of the mean. Other abbreviations as in Table 1.
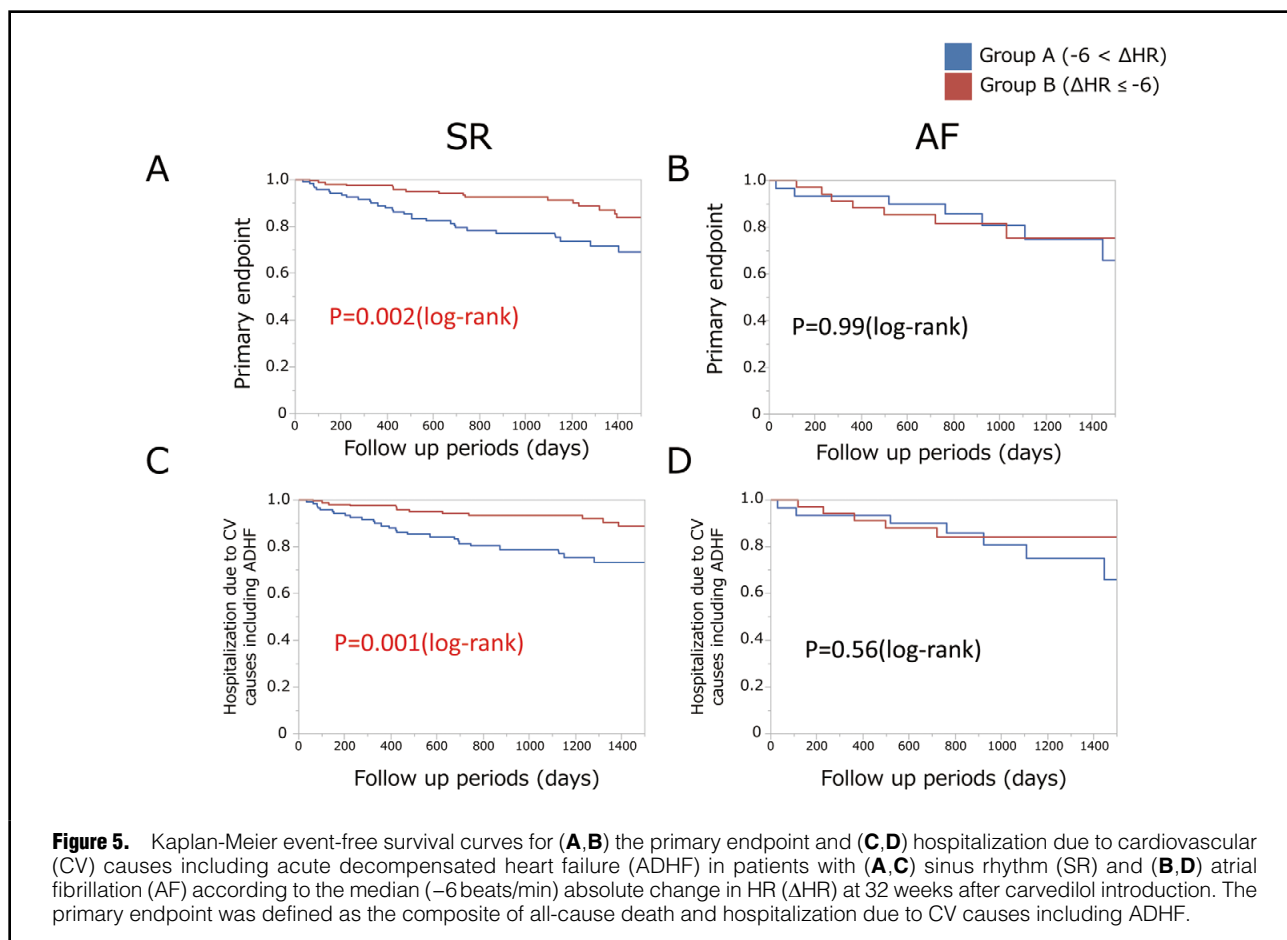

Figure 5. Kaplan-Meier event-free survival curves for (**A**,**B**) the primary endpoint and (**C**,**D**) hospitalization due to cardiovascular (CV) causes including acute decompensated heart failure (ADHF) in patients with (**A**,**C**) sinus rhythm (SR) and (**B**,**D**) atrial fibrillation (AF) according to the median (−6 beats/min) absolute change in HR (ΔHR) at 32 weeks after carvedilol introduction. The primary endpoint was defined as the composite of all-cause death and hospitalization due to CV causes including ADHF.

HR, although the older age and higher prevalence of anemia in the lower HR group might have affected those findings (data not shown).[17]

Multiple regression analysis was performed to determine the independent predictors of ΔLVEF over 56 weeks. In SR, ΔHR was an independent predictor for ΔLVEF whereas achieved dose of carvedilol was not (**Table 2**). In AF, neither ΔHR nor achieved dose of carvedilol predicted ΔLVEF.

During a median 2.9 years (IQR, 2.1–4.0 years) of follow up, SR-B was associated with a lower incidence of the primary endpoint (defined as the composite of all-cause death and hospitalization due to CV causes including ADHF), than SR-A (P=0.002, log-rank test; **Figure 5A**). SR-B was also associated with a lower incidence of hospitalization due to CV causes including ADHF (P=0.001,

log-rank test; **Figure 5C**). In the AF groups, however, such differences were not observed (**Figure 5B,D**). On Cox proportional hazard model analysis, ΔHR, but not achieved dose of carvedilol, was an independent predictor of primary endpoint in SR (**Table 3**). In contrast, neither ΔHR nor achieved dose of carvedilol predicted the primary endpoint in AF (**Table 3**).

Discussion

In the present study the main findings were as follows: (1) greater HR reduction by carvedilol was associated with more favorable LV reverse remodeling in SR but not in AF; (2) ΔHR was an independent predictor for ΔLVEF in SR but not in AF; (3) greater HR reduction by carvedilol

Table 3. Independent Predictors of the Primary Endpoint in HFrEF Patients[†]

	SR			AF		
	HR	95% CI	P-value	HR	95% CI	P-value
Age	1.02	0.99–1.05	0.19	0.94	0.88–1.01	0.09
Sex (F/M)	0.46	0.20–0.93	0.03	0.20	0.01–2.12	0.19
NYHA (III/II)	3.04	1.50–5.92	0.003	2.50	0.53–9.35	0.22
CAD	1.03	0.51–2.00	0.93	88.2	9.63–1,382	<0.0001
LVEF at baseline	0.996	0.96–1.04	0.84	1.17	1.01–1.37	0.04
Final dose of carvedilol	0.98	0.93–1.02	0.38	1.05	0.97–1.13	0.24
ΔHR	1.03	1.01–1.05	0.01	0.97	0.93–1.01	0.19

[†]Cox proportional hazard model analysis. Abbreviations as in Tables 1,2.

was associated with a more favorable long-term outcome in SR but not in AF; and (4) ΔHR was an independent predictor of the primary endpoint in SR but not in AF. This indicates that AF limits the benefit of HR reduction by carvedilol in HFrEF. To our knowledge, this is the first study to demonstrate a differential response to HR reduction by carvedilol (including LV reverse remodeling) between SR and AF in HFrEF patients.

Benefit From HR Reduction in HFrEF With SR
Beta-blockers have multifaceted effects on the pathophysiology of HF, such as amelioration of myocardial oxygen demand, of LV wall stress, of catecholamine-induced myocardial apoptosis and of arrhythmias. Also, carvedilol might exert its beneficial effect possibly through its antioxidant properties.[18] In the clinical setting the benefit of β-blockers is malinly correlated to HR reduction rather than reduction of blood pressure or dosage of β-blockers.[5,15] In a meta-analysis the improvement of LVEF during β-blocker treatment was shown to be correlated with change of HR.[6] It remains uncertain whether HR reduction might be attributed to the direct effect of β-blockers or to an indirect effect of improved hemodynamics or cardiac function. Ivabradine can also benefit HFrEF patients with SR through HR reduction by specifically inhibiting the I_f current in the sinoatrial node,[2,19] and its benefit was correlated with achieved HR.[20] This indicates that HR reduction per se can benefit HFrEF patients with SR.

Differential Benefit According to SR and AF
In the majority of the randomized controlled trials conducted in the 1980s through early 2000s on the effect of β-blockers on HFrEF, patients with concomitant AF were excluded or comorbid AF was not reported.[5] Therefore, data on the benefit of HR reduction in HFrEF with AF have been limited. In the CIBIS II and MERIT-HF studies, there was no mortality benefit from the β-blockers bisoprolol or metoprolol succinate compared with placebo in patients with HFrEF with AF.[10,11] In a meta-analysis of 10 randomized clinical trials that compared β-blockers with placebo, β-blockers were not associated with a mortality reduction in the HFrEF patients with AF.[12] Subsequent studies have reported no association between HR and survival in HFrEF patients with AF, although a benefit of β-blockers on clinical outcome was observed.[13,14] The present results are in line with those studies and further support the differing response to β-blocker HR reduction in HFrEF patients with AF in terms of LV reverse remodeling. HR is one of the factors that determines the dose of β-blockers in HFrEF.

According to the present results, however, HR might not be as useful in determining the optimal dose of carvedilol in HFrEF with concomitant AF.

The potential mechanisms that mediate the differing benefit of HR reduction between SR and AF remain uncertain. In the present study the HR data were obtained at rest, but obviously HR changes over time. In SR, resting HR might be somewhat correlated with the average HR during 24h, but the association might be weaker in AF, possibly because the response of HR at exercise is augmented, and it might differ substantially between individuals to a greater extent in AF compared with SR.[21] In the present study Holter ECG was recorded in only a small number of subjects (n=88 at baseline, 19 at 32 weeks and 14 at 56 weeks), and hence it could not be included in the statistical analysis. Exploration using average HR during 24h might provide further evidence on this issue. In the present study LV reverse remodeling was achieved even in patients with AF irrespective of HR reduction. The multifaceted effects of carvedilol mentioned earlier might also play an important role in LV reverse remodeling in HFrEF with AF, although we cannot provide any evidence on this matter given that the J-CHF study did not have a placebo group.

In a recent observational study of patients with new onset or worsening HFrEF, time-dependent change in HR was associated with the composite endpoint of death and ADHF hospitalization both in the patients with SR and those with AF.[14] The potential mechanisms of the conflict with the present study remain unknown. In that study the patients had new onset or worsening HF at baseline, whereas the present study enrolled stable HFrEF patients in the compensated phase. Also, besides β-blockers, digoxin was used in approximately 70% of patients with AF. This might lead to a reduced rate of the composite endpoint including ADHF hospitalization in HFrEF patients with AF who had greater reduction in HR.

Study Limitations
There are several important limitations in the present study. First, this study was conducted as a substudy of the J-CHF study in order to elucidate the differing benefit from HR reduction by carvedilol in HFrEF patients between SR and AF. The nature of the post hoc analysis can potentially include risk of bias. Second, the relatively small number of AF patients might have limited the statistical power to detect a difference between the groups. Third, as mentioned earlier, resting HR was used for the analysis, which might not precisely reflect average HR during 24h. Fourth, the subjects were divided into SR and AF groups based on

ECG at baseline. The prognostic impact of newly developed AF and chronic AF might differ in the setting of HF.[22–24] Information on AF patterns (i.e., paroxysmal, persistent or chronic) was not available in the present study. Further, the cardiac rhythm was not evaluated afterwards. Fifth, the present study does not provide any clues to the mechanistic link or causal relationship between cardiac rhythm (SR or AF) and the benefit from HR reduction by carvedilol such as LV reverse remodeling and subsequent clinical outcome. Accordingly, the effectiveness of rhythm control or conversion from AF to SR is uncertain from the findings of the present study, although a recent study reported the effectiveness of catheter ablation for AF on survival in patients with HFrEF.[25] Sixth, the presence of AF is associated with various kinds of comorbidities such as cognitive impairment or frailty.[26,27] These unmeasured factors might be potential confounding factors affecting the present results. Seventh, given that the J-CHF study enrolled the HFrEF patients more than 10 years ago, there may be some limitations in applying the present findings to current clinical practice. Finally, in the present study carvedilol was given to all subjects and it is uncertain whether the observed findings are generalizable to other kinds of β-blockers.

Conclusions

The response to HR reduction by carvedilol might differ in HFrEF between SR and AF. Further investigation is warranted to elucidate the detailed mechanisms.

Disclosures

T.Y. is a member of *Circulation Reports*' Editorial Team. The other authors declare no conflicts of interest.

Data Availability

This manuscript reports the results of clinical trials. The data will not be shared.

IRB Information

The J-CHF study was approved by the Ethics Committee of Hokkaido University Graduate School of Medicine, Hokkaido, Japan (318). The institutional review board of each participating institution approved the J-CHF study protocol.

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Supplementary Files

Please find supplementary file(s);
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