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RAPID COMMUNICATION

Effect of Ivabradine on Left Ventricular Reverse Remodeling in Relatively Stable Heart Failure Outpatients With Reduced Ejection Fraction

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Background: Elevations of resting heart rate (HR) in patients with heart failure (HF) with reduced ejection fraction (HFrEF) are often missed, resulting in some patients with an indication for ivabradine reportedly being missed.

Methods and Results: We studied 30 relatively stable HFrEF outpatients, and ivabradine was administered when regular follow-up echocardiography showed a resting HR ≥75 beats/min. Significant left ventricular reverse remodeling was observed 10.1±3.9 months after administration of ivabradine.

Conclusions: This finding may well make this procedure a potential new approach for preventing worsening of HF for relatively stable patients with HFrEF.

Key Words: Heart rate; Ivabradine; Left ventricular reverse remodeling

The detrimental effects of an increase in resting heart rate (HR) on cardiovascular mortality and morbidity of patients with heart failure (HF) with reduced ejection fraction (HFrEF) are well documented. High resting HR is a known marker of cardiovascular outcomes for patients with HFrEF, and 1-beat and 5-beat increases in resting HR augment the risk of cardiovascular death and HF hospitalization of HFrEF patients by 3% and 16%, respectively.[1] The positive effect of ivabradine, a selective sinus node I_f channel inhibitor, on cardiovascular events in symptomatic patients with HFrEF of left ventricular (LV) ejection fraction (LVEF) ≤35% and resting HR of ≥70 beats/min in sinus rhythm has been demonstrated by SHIFT (the Systolic Heart failure treatment with the IF inhibitor ivabradine Trial).[1] In addition, the Japanese SHIFT Phase III study (J-SHIFT) showed that the efficacy of ivabradine was similar to that observed in SHIFT for symptomatic patients with HFrEF of LVEF ≤35% and resting HR ≥75 beats/min in sinus rhythm.[2] However, the effect of ivabradine on LV reverse remodeling in symptomatic patients with HFrEF, especially in relatively stable outpatients with HFrEF, has not been studied and thus remains uncertain. Therefore, the aim of the present study was to investigate the effect of ivabradine on LV reverse remodeling for relatively stable outpatients with HFrEF at a specialist outpatient HF clinic.

Methods

Study Population

For the present study, 30 outpatients with HFrEF who had been treated with ivabradine at a specialist outpatient HF clinic of Kobe University Hospital between November 2019 and October 2023 were retrospectively enrolled. Preliminary exclusion criteria for the present study were: (1) history of HF hospitalization ≤3 months before administration of ivabradine; (2) advanced symptomatic HF, such as New York Heart Association (NYHA) functional class III or IV; or (3) atrial fibrillation. Indications for the administration of ivabradine were based on the current guideline of the Japanese Circulation Society,[3] specifically for symptomatic HF patients with reduced LVEF ≤35%, sinus rhythm, and resting HR ≥75 beats/min despite guideline-directed medical therapy.

All patients were given 5 mg/day ivabradine at the same time as baseline echocardiography. Doses were increased to 5, 10, and 15 mg/day, as determined by evaluation of resting HR and clinical symptoms. Patients were assessed every 2 or 3 weeks to attain the optimal dose. The target resting HR for the present study was approximately 60 beats/min. Other drugs were not changed from ivabradine administration until follow-up echocardiography. Physical examinations and blood tests were performed on the same day as the baseline echocardiography and follow-up echo-

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Table 1. Baseline Characteristics (n=30)	
Clinical characteristics	
Age (years)	66.6±14.3
Male sex	26 (86.7)
Body mass index (kg/m²)	1.6±0.2
SBP (mmHg)	108.3±11.8
Heart rate (beats/min)	80.4±4.6
Previous history of hospitalization for HF	5 (16.7)
Ischemic etiology	4 (13.3)
Blood examination	
Hemoglobin (mg/dL)	12.5±2.0
eGFR (mL/min/1.73 m²)	54.2±10.5
BNP (pg/dL)	92.5 [60.3–131.8]
NYHA functional class	
I	0 (0)
II	30 (100)
III	0 (0)
IV	0 (0)
Comorbidities	
Hypertension	6 (20)
Diabetes	6 (20)
Dyslipidemia	3 (10)
Atrial fibrillation	0 (0)
Medications	
ACE-i/ARB	9 (30)
ARNI	19 (63.3)
β-blockers	30 (100)
Dose of β-blocker (mg)	
Carvedilol	17.3±3.6
Bisoprolol	4.4±1.0
MRAs	28 (93.3)
SGLT2 inhibitors	17 (56.7)
Loop diuretics	10 (33.3)
Echocardiography data	
LV end-diastolic volume (mL)	168.2±43.0
LV end-systolic volume (mL)	119.7±39.6
LVEF (%)	29.0±6.7
LV mass index (mg/m²)	103.3±11.8
LA volume index (mL/m²)	43.0±12.1
E/e'	12.4±3.8
Mitral regurgitation (≥moderate)	7 (23.3)
Aortic stenosis (≥moderate)	0 (0)
Aortic regurgitation (≥moderate)	1 (3.3)

Data are presented as the mean±SD for normally distributed data, median [interquartile range] for non-normally distributed data, or as n (%). ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BNP, B-type natriuretic peptide; E, peak early diastolic mitral flow velocity; e', spectral pulsed-wave Doppler-derived early diastolic velocity from the septal mitral annulus; eGFR, estimated glomerular filtration rate; HF, heart failure; LA, left atrium; LV, left ventricular; LVEF, left ventricular ejection fraction; MRAs, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; SBP, systolic blood pressure; SGLT2, sodium-glucose cotransporter 2.

cardiography. The present study was approved by the local ethics committee of Kobe University Hospital Clinical and Translational Research Center (No. B240035) and was performed in accordance with the Declaration of Helsinki.

Echocardiography Examination

Echocardiography studies were performed before and 10.1±3.9 months after the administration of ivabradine. All echocardiography data were obtained using a commercially available echocardiography system. Standard echocardiography measurements were obtained in accordance with the current guidelines of the American Society of Echocardiography.[4]

Assessment of Resting HR

Resting HR was determined as the average HR during echocardiography.

Definition of Study Endpoint

The primary endpoint was defined as a comparison of LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LVEF at baseline and after administration of ivabradine.

Statistical Analysis

Continuous variables are expressed as the mean±SD for normally distributed data, and as the median with interquartile range (IQR) for data that were not normally distributed. Categorical variables are expressed as frequencies and percentages. Parameters of the enrollees between baseline and after administration of ivabradine were compared using paired t-tests or the Wilcoxon signed-rank test, depending on data distribution. Proportional differences were evaluated using Fisher's exact test. For all analyses, $P<0.05$ was considered statistically significant. All analyses were performed using commercially available software (MedCalc version 22.021; MedCalc Software, Mariakerke, Belgium).

Results

Baseline Characteristics

The baseline characteristics of all 30 patients with HFrEF are summarized in **Table 1**. The mean age was 66.6±14.3 years, 26 (87%) were male, and baseline systolic blood pressure was 108.3±27.2 mmHg. All patients were classified as NYHA functional class II. Mean LVEDV was 168.8±42.2 mL, mean LVESV was 122.0±36.3 mL, and mean LVEF was 28.3±5.4%. Resting HR declined significantly from 80.4±4.6 to 63.1±3.9 beats/min ($P<0.001$) 10.1±3.9 months after administration of ivabradine.

LV Reverse Remodeling Following Administration of Ivabradine

Results for the primary endpoint of LV reverse remodeling after administration of ivabradine are shown in **Figure**. Significant LV reverse remodeling was observed 10.1±3.9 months after administration of ivabradine (LVEDV: 168.8±42.2 vs. 148.6.3±43.2 mL, $P<0.001$; LVESV: 122.0±36.3 vs. 91.7±41.2 mL, $P<0.001$; LVEF: 28.3±5.4% vs. 37.0±10.1%, $P<0.001$). Other parameters before and after the administration of ivabradine are summarized in **Table 2**. The mean dose of ivabradine was 12.0±3.6 mg, with 16 (53.3%) patients receiving 15 mg, 10 (33.3%) patients receiving 10 mg, and 4 (13.3%) patients receiving 5 mg. Systolic

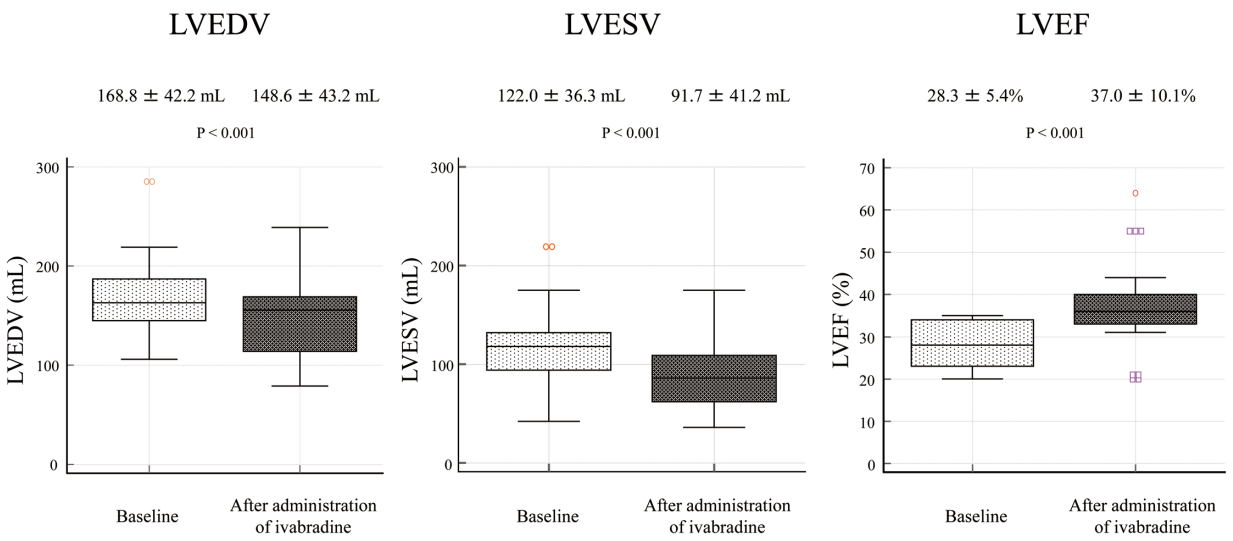

Figure. Results for the primary endpoint, showing that significant left ventricular (LV) reverse remodeling, comprising LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LV ejection fraction (LVEF), was observed 10.1±3.9 months after the administration of ivabradine. The boxes show the interquartile range, with the median value indicated by the horizontal line; whiskers show the range. Mean±SD values are given above the graphs.

Table 2. Parameters Before and After the Administration of Ivabradine

	Baseline	After administration of ivabradine	P value
SBP (mmHg)	108.3±11.8	110.8±10.2	<0.001
HR (beats/min)	80.4±4.6	63.1±3.9	<0.001
eGFR (mL/min/1.73 m^2)	54.2±10.5	53.1±11.1	0.353
BNP (pg/dL)	92.5 [60.3–131.8]	87.5 [60.0–120.0]	<0.001
Dose of ivabradine (mg)	–	12.0±3.6	–
15	–	16 (53.3)	–
10	–	10 (33.3)	–
5	–	4 (13.3)	–

Data are presented as the mean±SD for normally distributed data, median [interquartile range] for non-normally distributed data, or as n (%). HR, heart rate. Other abbreviations as in Table 1.

blood pressure increased significantly from 108.3±11.8 to 110.8±10.2 mmHg (P<0.001), and B-type natriuretic peptide was significantly (P<0.001) reduced from a median of 92.5 (IQR 60.3–131.8) to 87.5 (IQR 60.0–120.0) (pg/dL) after administration of ivabradine.

Discussion

The findings of the present study show that significant LV reverse remodeling was observed in relatively stable outpatients with HFrEF of NYHA Class II 10.1±3.9 months after administration of ivabradine.

Ivabradine for Patients With HFrEF

HF is a progressive disease characterized by periods of clinical stability interrupted by episodes of worsening signs and symptoms. These episodes of deterioration are recognized as a distinct phase in the natural history of the disease. This worsening of HF for patients with HFrEF is strongly associated with outcome,[5,6] so its prevention is very important. Quadruple medical therapy, comprising β-blockers, angiotensin receptor-neprilysin inhibitor, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter 2 inhibitors, is highly recommended for diminishing cardiovascular mortality and HF hospitalization for patients with HFrEF.[7,8] However, patients with HFrEF who have already received quadruple medical therapy sometimes experience worsening HF so that additional therapy consisting of the initiation of ivabradine should be reconsidered in order to reduce the residual clinical risk for patients with HFrEF and resting HR ≥75 beats/min.

Clinical Implications of the Present Study

The present study used relatively stable outpatients with HFrEF (NYHA Class II) and resting HR ≥75 beats/min at a specialist outpatient HF clinic. Ivabradine was administered when regular follow-up echocardiography showed a

resting HR ≥75 beats/min. Elevations in resting HR in patients with HFrEF are often missed. Thus, echocardiography should be performed regularly in patients with HFrEF because it effectively identifies patients with elevated HR, and resting HR needs to be constantly monitored during the examination. Current guidelines give ivabradine a Class IIa recommendation for symptomatic patients with HFrEF (LVEF ≤35%) and resting HR ≥70 beats/min[8,9] or ≥75 beats/min[3] and sinus rhythm despite guideline-directed medical therapy to reduce HF hospitalization and cardiovascular death. Although guidelines have been published to assist physicians and improve outcomes, there is evidence of gaps between recommendations and clinical practice, even in specialized settings. In addition, some patients with an indication for ivabradine are reportedly being missed. Findings by Jarjour et al[10] for 511 patients with HFrEF at a single HF clinic showed that when eligibility for ivabradine administration was set at a HR of >77 beats/min, 469 (91.8%) patients were not eligible. Of the remaining 42 candidates, only 19 (46.3%) received ivabradine, with the target dose reached in only 2 (10.5%) patients. In addition, administration for 5 (26.3%) patients was optimized, and another 5 remained undertitrated, leaving 9 patients with inappropriately low doses.[10] When eligibility was set at HR >70 beats/min, the results were similar for 61 eligible patients, 19 (31.2%) of whom received ivabradine, 5 (26.3%) were optimized, and 5 (26.3%) remained uptitrated, thus leaving 9 patients undertitrated.[10] Because the present study showed that significant LV reverse remodeling could be observed in outpatients with HFrEF and resting HR ≥75 beats/min, the need for ivabradine administration is likely to increase even more during the present HF pandemic.

Study Limitations

The present study was retrospective and comprised a small number of patients, so future prospective studies with larger patient populations will be needed to validate our findings. Although the target HR following ivabradine administration for patients with HFrEF and high resting HR is known, the target resting HR following ivabradine was approximately 60 beats/min in the present study. Some investigators have reported the utility of the length of the overlap between the E-wave and A-wave on transmitral Doppler echocardiography to determine the target HR to be attained following administration of ivabradine.[11,12] Finally, the frequency of prescription of angiotensin receptor-neprilysin inhibitor and sodium-glucose cotransporter 2 inhibitors was low in the present study because some patients were included before these drugs were added to the indications for patients with HFrEF.

Conclusions

Following administration of ivabradine, significant LV reverse remodeling was observed in relatively stable outpatients with sinus rhythm of HFrEF and HR ≥75 beats/min. This finding may well make this procedure a potential new approach for preventing worsening of HF for relatively stable patients with HFrEF.

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Disclosures

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IRB Information

This study was approved by the Kobe University Hospital Clinical and Translational Research Center (Reference No. B240035).

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