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ORIGINAL ARTICLE
Heart Failure

Efficacy and Safety of Ivabradine in Japanese Patients With Chronic Heart Failure

— J-SHIFT Study —

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on behalf of the J-SHIFT Study Investigators

Background: Increased heart rate (HR) is an independent risk factor for cardiovascular outcomes in chronic heart failure (HF). Ivabradine, an I_f inhibitor, improved outcomes in patients with HF and reduced ejection fraction (HFrEF) in the SHIFT study. We evaluated its efficacy and safety in Japanese HFrEF patients in a randomized, double-blind, placebo-controlled phase III study: the J-SHIFT study. The main objective was to confirm a hazard ratio of <1 in the primary composite endpoint of cardiovascular death or hospital admission for worsening HF.

Methods and Results: Patients with NYHA functional class II–IV, left ventricular EF ≤35%, and resting HR ≥75 beats/min in sinus rhythm under optimal medical therapy received ivabradine (n=127) or placebo (n=127). Mean reduction in resting HR was significantly greater in the ivabradine group (15.2 vs. 6.1 beats/min, P<0.0001). However, symptomatic bradycardia did not occur. A total of 26 (20.5%) patients in the ivabradine group and 37 (29.1%) patients in the placebo group had the primary endpoint event (hazard ratio 0.67, 95% CI 0.40–1.11, P=0.1179) during median follow-up of 589 days. Mild phosphenes were reported in 8 (6.3%) patients in the ivabradine group and 4 (3.1%) patients in the placebo group (P=0.3760).

Conclusions: The J-SHIFT study supported the efficacy and safety of ivabradine for Japanese HFrEF patients, in accord with the SHIFT study.

Key Words: Chronic heart failure; Heart rate; Ivabradine; Japanese; Left ventricular ejection fraction

An elevated resting heart rate (HR) is reported to be an independent risk factor for death and cardiovascular outcomes in patients with heart failure (HF).[1] Ivabradine is a pure HR-lowering agent that blocks the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel responsible for the cardiac pacemaker I_f current in the sinoatrial node.[2] The Systolic Heart failure

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treatment with the I_f inhibitor ivabradine Trial (SHIFT) showed the efficacy and safety of ivabradine in patients with HF and reduced ejection fraction (HFrEF).[3] A phase II trial for Japanese patients with HFrEF demonstrated that ivabradine resulted in a significant reduction in resting HR compared with placebo,[4] but the efficacy and safety of ivabradine remain unestablished in Japanese patients with HFrEF.

The Japanese SHIFT phase III study (J-SHIFT) was conducted to investigate the efficacy and safety of ivabradine on Japanese patients with HFrEF compared with placebo. Based on the results of the SHIFT study, thousands of patients are required to verify the statistically significant superiority of ivabradine to placebo for the mortality and morbidity endpoints. However, it was unrealistic to enroll this number of patients in a single-country trial in Japan. Therefore, the J-SHIFT study was designed to evaluate the consistency of results with those from the SHIFT study. Consistency was predefined as a point estimate of the hazard ratio <1 in the primary composite endpoint of cardiovascular death or hospital admission for worsening HF. This concept is similar to that used in the J-EMPHASIS trial, a randomized double-blind placebo-controlled study, to determine the similar efficacy and safety of eplerenone in Japanese patients as in the EMPHASIS trial.[5]

Methods

Study Design and Patients

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in Japanese patients with HFrEF. The study consisted of 2 periods: a 2-week observation period followed by a treatment period of at least 52 weeks, during which patients received either ivabradine or placebo (**Supplementary Figure 1**). Patients were enrolled from 146 institutions in Japan between October 2015 and August 2018 (**Supplementary Appendix**).

Key inclusion and exclusion criteria are shown in **Supplementary Table 1**. Briefly, eligible patients were ≥20 years of age, had stable symptomatic chronic HF of New York Heart Association (NYHA) functional class II–IV, left ventricular EF (LVEF) ≤35%, resting HR ≥75 beats/min in sinus rhythm, received optimal treatment for HF according to the Japanese Guidelines for Treatment of Chronic Heart Failure,[6,7] and had a history of hospital admission for worsening HF within the preceding 52 weeks. Exclusion criteria included myocardial infarction within the previous 8 weeks, ventricular or atrioventricular pacing >40% of 24 h, persistent atrial fibrillation or flutter, and symptomatic hypotension. The inclusion and exclusion criteria for the J-SHIFT study were similar to those for the SHIFT study, except for the baseline resting HR ≥75 beats/min in J-SHIFT compared with ≥70 beats/min in the SHIFT study.[3] This modification was based on the post-hoc subgroup analysis in the SHIFT study demonstrating consistent and statistically significant improvement in all clinical events, including all-cause and cardiovascular death, in patients with baseline resting HR ≥75 beats/min.[8] Changes in drug treatments for chronic HF were not allowed in the 4 weeks prior to the initiation of the observation period or during the treatment period, except for the occurrence of adverse events (AEs). Medications, including β-blockers other than carvedilol or bisoprolol fumarate, non-dihydropyridine calcium-channel blockers, class I antiarrhythmics, moderate or strong inhibitors of cytochrome P450 3A4, cytochrome P450 3A4 inducers, and any unapproved drugs were not permitted during the observation or treatment periods.

The study conformed to the principles outlined in the Declaration of Helsinki[9] and Good Clinical Practice guidelines[10] and was approved by the ethical committee or review board of each institution. All patients provided written informed consent before study enrollment.

Randomization and Masking

After the 2-week observation period to confirm the inclusion and exclusion criteria, patients were randomly allocated to either the ivabradine or placebo group at 1:1. A minimization method for dynamic allocation was used with adjustment for study site, baseline resting HR (≥85 and <85 beats/min), and β-blocker dose before study treatment (0, >0–<50, and ≥50% of the target dose of carvedilol 20 mg/day and bisoprolol 5 mg/day) to balance baseline covariates. Patients and investigators were masked to treatment allocation, and study medications (ivabradine or placebo) were the same size and color.

Study Procedures (Supplementary Figure 1)

Ivabradine or placebo was started at 2.5 mg twice daily (BID). The dose was adjusted at each visit in the range of 2.5–7.5 mg BID according to dose adjustment criteria; the dose was increased if the resting HR was higher than 60 beats/min, maintained if between 50 and 60 beats/min, decreased if lower than 50 beats/min or patients had signs or symptoms related to bradycardia, and discontinued if lower than 50 beats/min or the patient had signs or symptoms related to bradycardia at the lowest dose. All patients were treated with the study drug for a minimum 52 weeks and followed until the 52-week follow-up of the last enrolled patient.

At every visit during the treatment period, patients underwent a physical examination and an assessment of NYHA functional class, resting HR measured by 12-lead ECG, vital signs, B-type natriuretic peptide (BNP), N-terminal prohormone of BNP (NT-proBNP), and laboratory tests. LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LVEF measured by echocardiography using the modified Simpson's method were measured at 2 months, and subsequently every 6 months. The occurrence of prespecified clinical events, including death or hospital admission for any cause, was recorded. AEs were recorded throughout the treatment period. When the study drug was discontinued because of AEs, prespecified clinical events were recorded until study completion.

Study Endpoints

The primary endpoint was the composite of cardiovascular death or hospital admission for worsening HF, as in the SHIFT study.[3] The secondary endpoints were all-cause, cardiovascular, or HF death; hospital admission for all causes, cardiovascular causes, or worsening HF, and a composite of cardiovascular death, hospital admission for worsening HF, or hospital admission for non-fatal myocardial infarction. Changes in resting HR, NYHA functional class, LVEDV index, LVESV index, LVEF, BNP, and NT-proBNP were also assessed. Safety endpoints included AEs including vital signs, laboratory tests, and 12-lead ECG. An endpoint adjudication committee, independent from the sponsor and investigators, evaluated all clinical events according to prespecified definitions in a

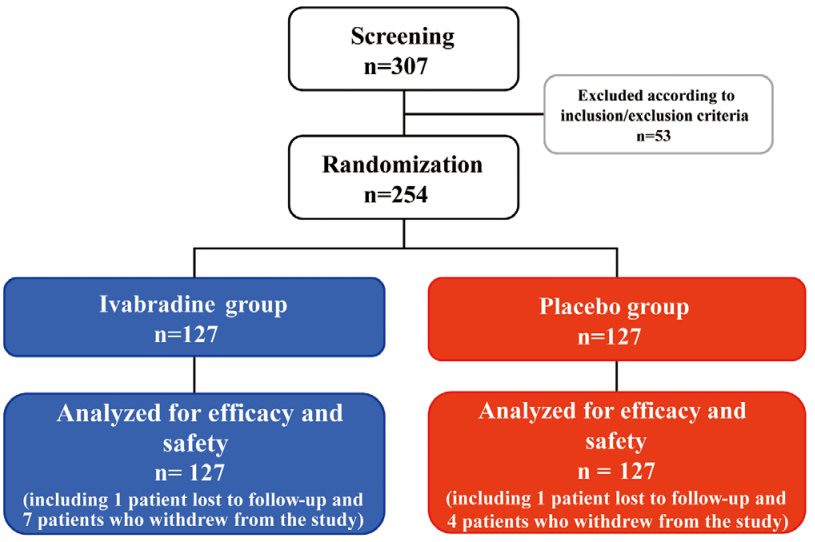


Figure 1. Study patient flow. Screened patients entered the 2-week observation period for confirmation of the inclusion or exclusion criteria.

blinded manner. All HRs, BNP, and NT-proBNP were measured by central laboratories.

Statistical Analysis

The aim of the J-SHIFT study was to confirm numerical improvement in the primary composite endpoint of cardiovascular death or hospital admission for worsening HF as a point estimate of the hazard ratio <1 because of feasibility. SAS version 9.3 software (SAS Institute, Inc., Cary, NC, USA) was used for all statistical analyses. Patients' baseline characteristics, and categorical and continuous data were compared between groups using chi-square and t test, respectively. HR, LVEDV index, LVESV index, LVEF, BNP, NT-proBNP, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were compared using analysis of covariance (ANCOVA). NYHA functional class was analyzed using chi-square test. The primary and secondary endpoints were analyzed using the Kaplan-Meier method (curves, median and 95% confidence interval [CI]), Cox proportional hazards model (hazard ratios, two-sided 95% CI) with treatment group as a factor, and resting HR and percentage of the target β-blocker dose at baseline as covariates. The consistency of the treatment effects was assessed among subgroups. The effect in each subgroup was analyzed using a Cox proportional hazard model with treatment group as a factor, and resting HR and percentage of the target β-blocker dose at baseline as covariates. P-values were calculated by adding the interaction term between the treatment groups and the subgroup status to the Cox model for primary composite endpoint. Incidence of AEs was analyzed using Fisher's exact test. All randomized patients were analyzed for efficacy. All study drug-treated patients after randomization were analyzed for safety.

The J-SHIFT study was designed to treat all the patients with the study drug for a minimum of 52 weeks and follow until 52 weeks from when the last patient was enrolled. This was aimed to collect as many clinical endpoints as possible. The sample size and the duration of follow-up were determined to ensure the statistical power to observe the positive trend (hazard ratio <1) in the primary composite endpoint, not to confirm statistical significance. The estimated number of patients required for the present study was 100 per group and assuming a 20% occurrence of study discontinuation or dropouts. The target patient number was calculated to be 125 patients per group.

Results

Patients' Characteristics

The study patient flow is shown in **Figure 1**: 307 patients were screened and entered the observation period; 53 patients were excluded according to the inclusion/exclusion criteria. Thus, 254 patients were enrolled and randomly assigned to the treatment groups: 127 patients in the ivabradine group and 127 patients in the placebo group. All patients enrolled into the study were analyzed for both efficacy and safety; 2 (0.8%) patients were lost during follow-up and 11 (4.3%) patients discontinued the study. These patients were censored at their last contact time.

The baseline characteristics were well balanced between the ivabradine and placebo groups (**Table 1**). The mean age was 60.6±13.5 years, and 209 (82.3%) patients were men. Mean resting HR was 82.4±7.7 beats/min and LVEF was 27.2±5.7%. The primary cause of HF was ischemic in 99 (39.0%) and non-ischemic in 155 (61.0%) patients. Most patients (202 [79.5%] patients) were in NHYA functional class II and 52 (20.5%) patients were in NHYA functional class III or IV. Angiotensin-converting enzyme (ACE) inhibitor and/or angiotensin receptor blocker (ARB) was used in 174 (68.5%) patients, β-blocker in 242 (95.3%) patients, mineralocorticoid receptor antagonist (MRA) in 197 (77.6%) patients, diuretic in 230 (90.6%) patients, and digitalis in 19 (7.5%) patients. β-blocker was used in 127 (50.0%) patients with at least 50% of the target dose defined by the guidelines,[7] and in 49 (19.3%) patients with the target dose. Predominant reasons for not receiving the target dose of β-blocker were hypotension (59.6%), decompensated HF (19.7%), dizziness (9.8%), and fatigue (8.8%). The reasons among 12 patients for not having β-blockers included bronchial asthma (25.0%) and decompensated HF (25.0%).

These baseline characteristics were also generally similar

Table 1. Baseline Characteristics of the Study Population

	Ivabradine group (n=127)	Placebo group (n=127)	P value*
Age (years)	61.2±13.3	60.1±13.7	0.5128
Sex (male)	107 (84.3)	102 (80.3)	0.4113
BMI (kg/m^2)	24.6±4.9	25.4±5.7	0.2302
HR (beats/min)	82.1±7.2	82.7±8.1	0.5531
SBP (mmHg)	115.3±18.1	116.4±18.5	0.6344
DBP (mmHg)	70.8±11.8	71.6±12.5	0.6000
LVEF (%)	27.9±5.3	26.6±6.1	0.0680
BNP (pg/mL)	334.5±400.0	410.8±529.8	0.1962
NT-proBNP (pg/mL)	1,940.0±2,753.3	1,920.7±2,198.3	0.9506
eGFR (mL/min/1.73 m^2)	65.3±26.3	66.3±24.0	0.7617
NYHA functional class			0.9497
II	100 (78.7)	102 (80.3)	
III	25 (19.7)	23 (18.1)	
IV	2 (1.6)	2 (1.6)	
Duration of HF (years)	5.4±5.9	4.3±5.0	0.1422
Primary cause of HF			0.8976
Ischemic	49 (38.6)	50 (39.4)	
Non-ischemic	78 (61.4)	77 (60.6)	
Medical history			
Hypertension	52 (40.9)	57 (44.9)	0.6122
Diabetes mellitus	67 (52.8)	56 (44.1)	0.2092
Dyslipidemia	90 (70.9)	90 (70.9)	1.0000
MI	27 (21.3)	39 (30.7)	0.1151
Angina pectoris	27 (21.3)	31 (24.4)	0.6541
Atrial fibrillation/flutter	12 (9.4)	11 (8.7)	1.0000
Medications			
ACE inhibitor	57 (44.9)	67 (52.8)	0.2585
ARB	31 (24.4)	20 (15.7)	0.1167
ACE inhibitor and/or ARB	88 (69.3)	86 (67.7)	0.8926
Diuretic (excluding MRA)	114 (89.8)	116 (91.3)	0.8306
MRA	106 (83.5)	91 (71.7)	0.0347
Digitalis	10 (7.9)	9 (7.1)	1.0000
β-blocker	122 (96.1)	120 (94.5)	0.7689
% of the target β-blocker dose†			0.9660
0	5 (3.9)	7 (5.5)	
>0–<50	58 (45.7)	57 (44.9)	
50–<100	39 (30.7)	39 (30.7)	
100	25 (19.7)	24 (18.9)	

Data are mean±SD or number of patients (%). *Chi-square test for categorical variables and analysis of variance for continuous variables. †Target β-blocker dose: carvedilol 20 mg/day and bisoprolol 5 mg/day. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, heart rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.

to those in the SHIFT study, except for higher resting HR (82.4 vs. 79.9 beats/min), because of the difference in the inclusion criteria of resting HR (≥75 in J-SHIFT vs. ≥70 beats/min in the SHIFT study), higher prevalence of NYHA functional class II (79.5% vs. 48.7%), lower ischemic cause of HF (39.0% vs. 67.9%), lower prevalence of hypertension (42.9% vs. 66.3%), higher prevalence of diabetes mellitus (48.4% vs. 30.4%), lower history of myocardial infarction (26.0% vs. 56.4%), lower use of ACE inhibitor and/or ARB (68.5% vs. 91.1%), higher use of MRA (77.6% vs. 60.3%), and lower use of digitalis (7.5% vs. 21.8%) (**Supplementary Table 2**). The percentage distribution of the target β-blocker dose was similar between the studies (**Supplementary Table 2**).

Study Drug Administration and Follow-up

There was no difference in treatment adherence, which was greater than 98% in each group. The median treatment duration was 561 and 549 days in the ivabradine and placebo groups, respectively (P=0.3247). The mean dose in the ivabradine group was 6.4±1.8 mg BID at 6 weeks, 6.7±1.8 mg BID at 56 weeks, and 6.2±2.3 mg BID at the end of treatment. At the end of treatment in the ivabradine group, 90 (70.9%) patients were on the highest dose of

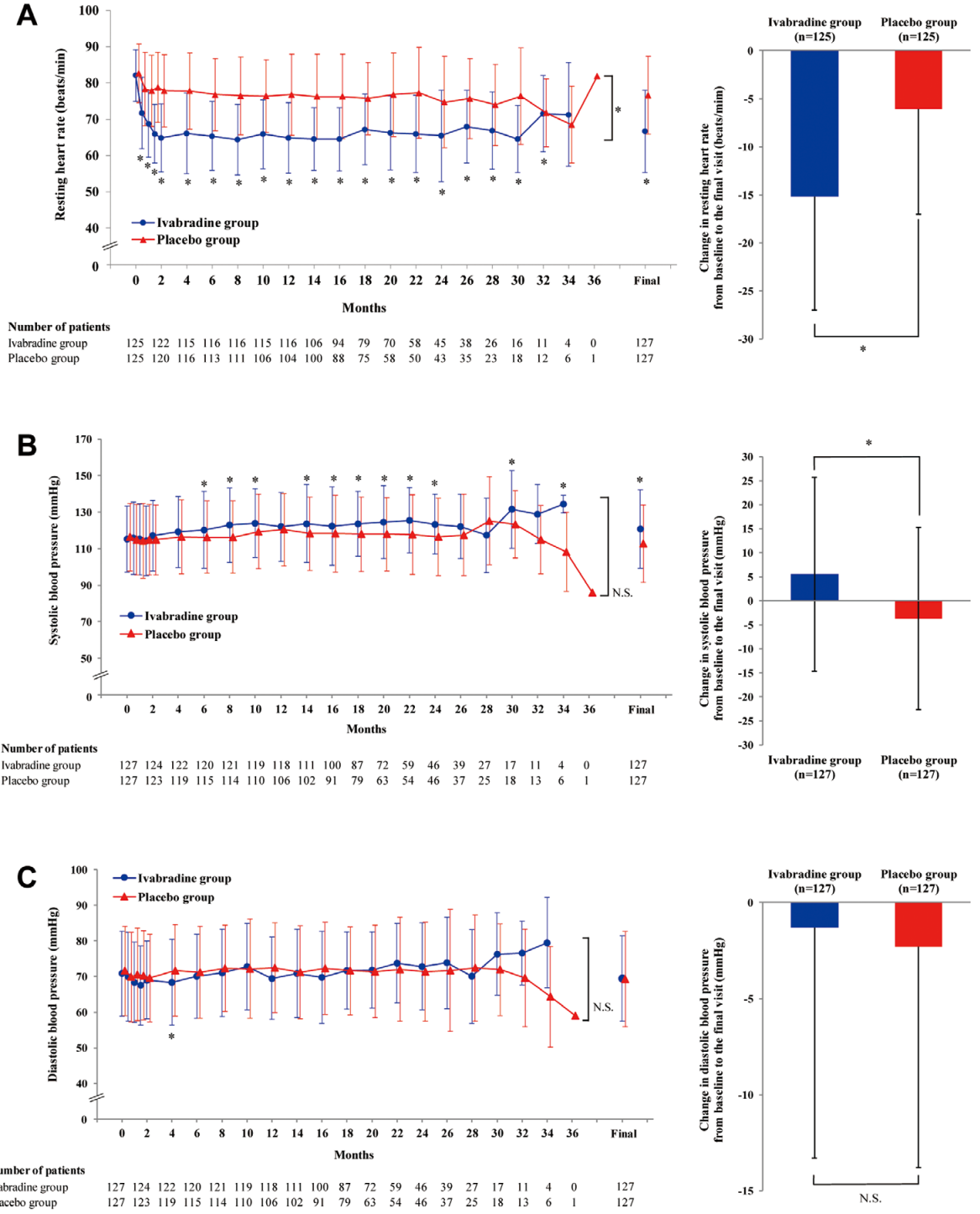
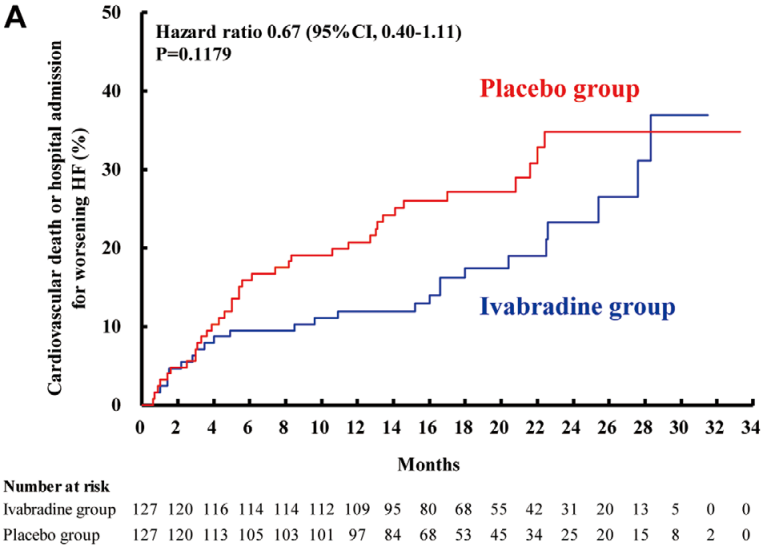


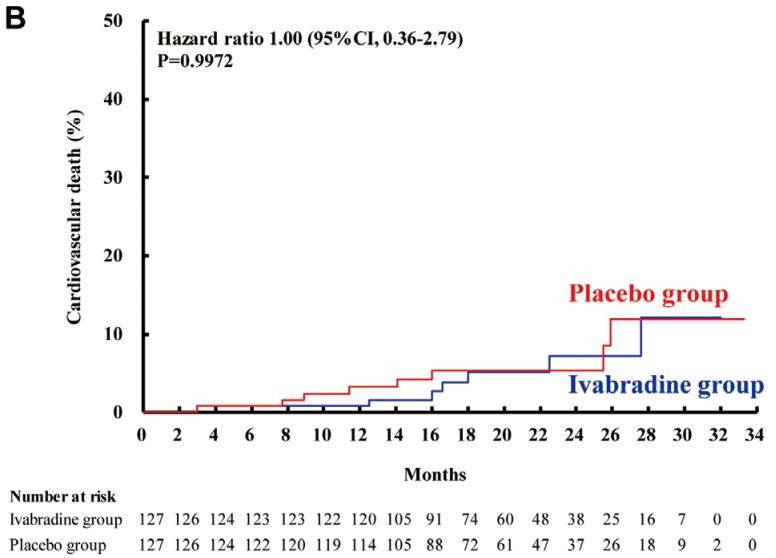
Figure 2. Time-dependent changes in (**A**) resting heart rate, (**B**) systolic blood pressure, and (**C**) diastolic blood pressure during the treatment. Data are shown as mean±SD. N.S., P≥0.05 vs. the placebo group at each time point or in the mean change from baseline. *P<0.05 vs. the placebo group at each time point or in the mean change from baseline.

7.5 mg BID, 20 (15.7%) patients were on 5 mg BID, and 7 (5.5%) patients were on 2.5 mg BID. A total of 11 (8.7%) patients in the ivabradine and 20 (15.7%) patients in the placebo group discontinued the study drug treatment. The median duration of follow-up was 582 and 589 days in the ivabradine and placebo groups, respectively (P=0.9091).

HR and BP

Resting HR was significantly reduced in the ivabradine group compared with the placebo group (P<0.0001)





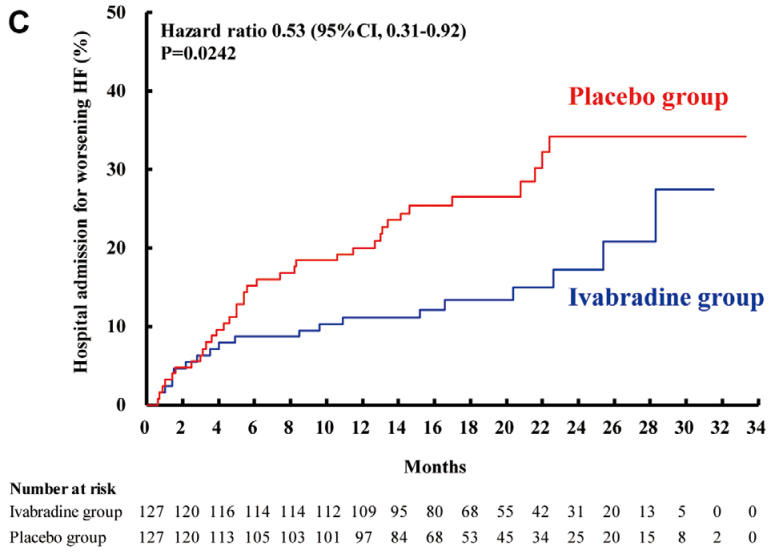


Figure 3. Kaplan-Meier cumulative event curves for (**A**) the primary composite endpoint of cardiovascular death or hospital admission for worsening heart failure, (**B**) cardiovascular death, and (**C**) hospital admission for worsening heart failure. Censoring data are not displayed. CI, confidence interval.

Table 2. Primary and Secondary Endpoints of J-SHIFT

Efficacy endpoints	Ivabradine group (n=127)	Placebo group (n=127)	Hazard ratio† (95% CI)	P value†
Primary composite endpoint				
Cardiovascular death or hospital admission for worsening HF	26 (20.5)	37 (29.1)	0.67 (0.40–1.11)	0.1179
Secondary endpoints				
All-cause death	9 (7.1)	9 (7.1)	1.15 (0.45–2.94)	0.7669
Cardiovascular death	7 (5.5)	8 (6.3)	1.00 (0.36–2.79)	0.9972
HF death	1 (0.8)	6 (4.7)	0.20 (0.02–1.70)	0.1405
Hospital admission for all causes	55 (43.3)	63 (49.6)	0.85 (0.59–1.22)	0.3649
Hospital admission for worsening HF	20 (15.7)	36 (28.3)	0.53 (0.31–0.92)	0.0242
Hospital admission for cardiovascular causes	36 (28.3)	48 (37.8)	0.73 (0.47–1.12)	0.1475
Cardiovascular death, hospital admission for worsening HF, or hospital admission for non-fatal MI	26 (20.5)	37 (29.1)	0.67 (0.40–1.11)	0.1179

Data are number of events (%). †Cox proportional hazards analysis with baseline resting HR and percentage of the target β-blocker dose as covariates. CI, confidence interval. Other abbreviations as in Table 1.

(**Figure 2A**). Respective mean resting HR for the ivabradine and placebo groups was 82.1±7.2 and 82.7±8.1 at baseline, 66.0±8.1 and 78.8±9.6 at 6 weeks, 64.6±8.6 and 76.3±11.7 at 56 weeks, and 66.7±11.4 and 76.6±10.7 beats/min at the final visit. Mean reduction in resting HR from baseline was significantly greater in the ivabradine group at 6 (−15.9±8.4 vs. −4.0±9.0 with a mean difference of −11.9±1.1 beats/min, P<0.0001), 56 weeks (−17.3±10.1 vs. −6.7±10.4 with a mean difference of −10.5±1.4 beats/min, P<0.0001), and the final visit (−15.2±11.8 vs. −6.1±10.9 with a mean difference of −9.2±1.4 beats/min, P<0.0001).

SBP tended to increase (P=0.0802) and its mean change from baseline to the final visit significantly increased in the ivabradine group compared with the placebo group (5.5±20.2 vs. −3.7±19.0 mmHg, P<0.0001) (**Figure 2B**). In contrast, DBP did not differ between the groups (P=0.5000) (**Figure 2C**).

Efficacy

The primary composite endpoint of cardiovascular death or hospital admission for worsening HF occurred at a lower rate in the ivabradine than in the placebo group (20.5 vs. 29.1%). This difference did not reach statistical significance (P=0.1179); however, the hazard ratio was <1 (0.67; 95% CI: 0.40–1.11) (**Figure 3A**; **Table 2**). The effects of ivabradine on the primary composite endpoint were consistent across both the prespecified and post-hoc subgroups (**Figure 4**). Importantly, these results were consistent across subgroups of % of target β-blocker dose (0, >0–<25, 25–<50, 50–<100, ≥100%). The rate of cardiovascular death was similar (5.5% vs. 6.3%; hazard ratio 1.00, 95% CI: 0.36–2.79, P=0.9972); however, that of hospital admission for worsening HF was significantly lower in the ivabradine group than in the placebo group (15.7% vs. 28.3%; hazard ratio 0.53, 95% CI: 0.31–0.92, P=0.0242) (**Figure 3B**,**C**; **Table 2**).

The distribution of NYHA functional class did not differ between the groups at 12, 24 months, or the final visit (P=0.8772, 0.5219 and 0.1914, respectively) (**Supplementary Figure 2A**). However, the proportion of patients with improved, unchanged, and worsened NYHA functional class from baseline to the final visit differed between the ivabradine and the placebo groups (P=0.0316) (**Supplementary Figure 2B**), showing that more patients in the ivabradine group had improved or not changed NYHA functional class at the final visit.

LVEF significantly increased from 27.9±5.3% at baseline to 38.9±12.8% at the final visit in the ivabradine group compared with the placebo group, in which LVEF increased from 26.6±6.1% to 33.3±13.0% (P=0.0004) (**Figure 5A**). Mean change in LVEF from baseline to the final visit was significantly greater in the ivabradine group (11.1±10.7 vs. 6.6±11.9, P<0.0001). LVESV index was significantly reduced in the ivabradine group compared with the placebo group (P=0.0372), but the LVEDV index did not differ between the groups (P=0.1312) (**Figure 5B**,**C**). However, the reduction from baseline to the final visit was significantly greater in the ivabradine group in both LVEDV index and LVESV index (**Figure 5B**,**C**).

There was no significant difference in the changes in plasma BNP and NT-pro BNP levels between the groups (**Supplementary Figure 3**).

Relationship Among HR, LV Function, and Outcomes

The primary composite endpoint of cardiovascular death or hospital admission for worsening HF was compared between subgroups according to the degree of median HR reduction at 6 weeks from baseline (>16 beats/min, n=56 vs. ≤16 beats/min, n=64 within the ivabradine group). It tended to be lower in patients with HR reduction >16 beats/min compared with those ≤16 beats/min (hazard ratio 0.69, 95%: CI 0.28–1.69, P=0.4161), which, however, did not reach statistical significance (**Supplementary Figure 4A**). These results were mainly driven by the reduction in cardiovascular death (hazard ratio 0.07, 95% CI: 0.00–1.22, P=0.0677) rather than hospital admission for worsening HF (hazard ratio 1.09, 95% CI: 0.41–2.93, P=0.8647) (**Supplementary Figure 4B**,**C**).

In the pooled ivabradine and placebo groups, the changes in LVEF and LVESV index were significantly greater in patients with median HR reduction >11 beats/min (9.5±10.0% vs. 6.6±9.7%, P=0.0252 for LVEF and −15.7±21.6 vs. −8.1±27.0 mL/m^2, P=0.0187 for LVESV index) (**Supplementary Figure 5A**,**C**). In addition, there was a significant linear correlation between the changes in HR and those in LVEF (r=−0.163, P=0.0150) and LVESV index (r=0.151, P=0.0249). Similar to the pooled ivabradine and placebo groups, the change in LVESV index was

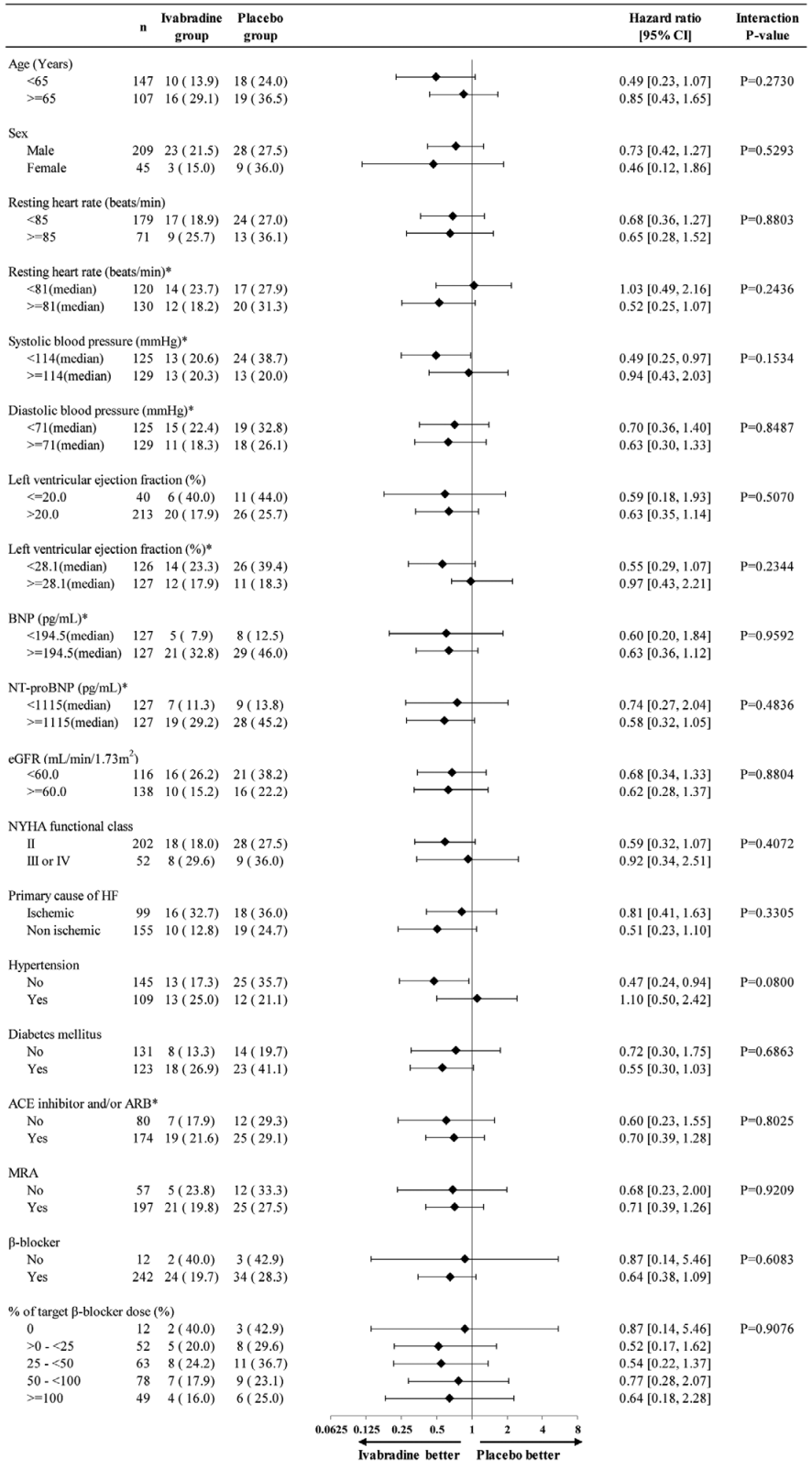


Figure 4. Hazard ratios for primary composite endpoint according to subgroups. Data are number (%) of patients with first events. Target β-blocker dose: carvedilol 20 mg/day and bisoprolol 5 mg/day. *Post-hoc analysis. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BNP, B-type natriuretic peptide; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal prohormone of BNP; NYHA, New York Heart Association.

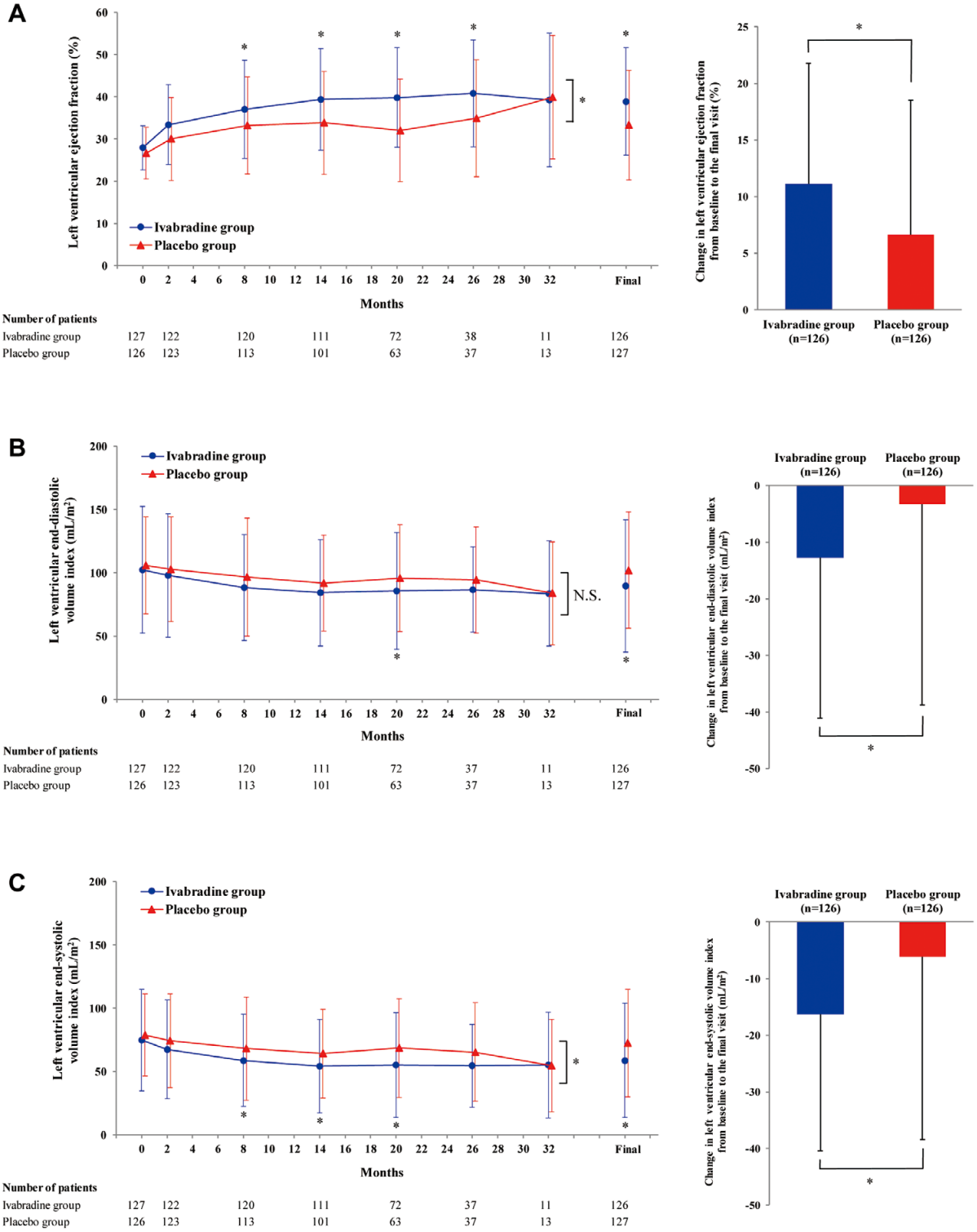


Figure 5. Changes in (**A**) left ventricular ejection fraction, (**B**) left ventricular end-diastolic volume index, and (**C**) left ventricular end-systolic volume index. Data are shown as mean±SD. N.S., P≥0.05 vs. the placebo group in the mean change from baseline. *P<0.05 vs. the placebo group at each time point or in the mean change from baseline.

Table 3. Incidence of AEs

	AEs			AEs leading to treatment discontinuation		
	Ivabradine group (n=127)	Placebo group (n=127)	P value*	Ivabradine group (n=127)	Placebo group (n=127)	P value*
All	119 (93.7)	116 (91.3)	0.6344	11 (8.7)	10 (7.9)	1.0000
HF**	31 (24.4)	49 (38.6)	0.0214	4 (3.1)	6 (4.7)	0.7489
Phosphenes	8 (6.3)	4 (3.1)	0.3760	0	0	–
Atrial fibrillation	3 (2.4)	7 (5.5)	0.3339	0	0	–
Asymptomatic bradycardia	1 (0.8)	1 (0.8)	1.0000	0	0	–

Data are n (%). *Fisher's exact test. **HF, acute HF, chronic HF, and congestive HF were merged into HF. AE, adverse event; HF, heart failure.

significantly greater in patients with median HR reduction >16 beats/min also in the ivabradine group (−19.9±20.0 vs. −11.3±19.3 mL/m^2, P=0.0446) (**Supplementary Figure 5F**).

To explore the effect of echocardiographic changes on clinical outcomes, the patients in the ivabradine group were divided according to median change in LVEF at 8 months (≥7.9%, n=60 vs. <7.9%, n=60). The incidence of the primary composite endpoint of cardiovascular death and hospital admission for worsening HF was significantly lower in patients with a greater increase in LVEF (hazard ratio 0.18, 95% CI: 0.06–0.55, P=0.0025) (**Supplementary Figure 6A**). Similar results were also obtained in LVEDV index (hazard ratio 0.24, 95% CI: 0.08–0.66, P=0.0057) and LVESV index (hazard ratio 0.12, 95% CI: 0.03–0.41, P=0.0007) (**Supplementary Figure 6B**,**C**).

Safety

The incidence of AEs did not differ between the groups (93.7% vs. 91.3%, P=0.6344) and that of AEs leading to treatment discontinuation was also similar between the groups (8.7% vs. 7.9%, P=1.000) (**Table 3**). The most common AE was HF, which occurred less in the ivabradine group (24.4% vs. 38.6%, P=0.0214), consistent with the efficacy results (**Figure 2**; **Table 2**). Phosphenes were observed in 8 patients (6.3%) in the ivabradine group and in 4 (3.1%) in the placebo group (P=0.3760). They were mild and did not need treatment discontinuation in either group. Incidence of atrial fibrillation tended to be lower in the ivabradine group (2.4 vs. 5.5%), but did not reach statistical significance (P=0.3339). In each group, 1 case of asymptomatic bradycardia (0.8%) was reported. No cases of symptomatic bradycardia were reported in either group.

There were no clinically significant changes in vital signs, laboratory parameters, or 12-lead ECG including QTc interval (data not shown).

Discussion

The J-SHIFT study demonstrated that ivabradine improved the primary composite endpoint of cardiovascular death or hospital admission for worsening HF in Japanese patients with NYHA functional class II–IV, LVEF ≤35%, and resting HR ≥75 beats/min in sinus rhythm under optimal medical therapy with a hazard ratio of 0.67 (95% CI: 0.40–1.11), confirming similar efficacy with the SHIFT study[3] results (**Figure 3**; **Table 2**).

The effects of ivabradine on the primary composite endpoint in the J-SHIFT study were mainly from a reduction in hospital admission for worsening HF (hazard ratio 0.53) rather than cardiovascular death (hazard ratio 1.00) (**Figure 3**; **Table 2**), consistent with the SHIFT study (hazard ratio: 0.74 for hospital admission for worsening HF and 0.91 for cardiovascular death).[3] In addition, ivabradine reduced most of the cardiovascular endpoints, including HF death, hospital admission for all causes, cardiovascular causes, and worsening HF, and the secondary composite endpoint (**Table 2**). These results were also similar to those observed in the SHIFT study.[3] Overall, the J-SHIFT study confirmed that ivabradine could provide similar improvements in clinical outcomes in Japanese HFrEF patients also, as observed in the SHIFT study.

The baseline characteritics of the studied patients were similar between the J-SHIFT and SHIFT studies except for the primary cause of HF and NYHA distribution (**Supplementary Table 2**). NYHA functional class was lower and non-ischemic cause was higher in Japanese patients, in line with previous clinical trials and registries.[4,11] Despite these differences between the J-SHIFT and SHIFT studies, prespecified subgroup analyses in the SHIFT and J-SHIFT studies showed that neither factor influenced the effects of ivabradine on the primary composite endpoint.[3]

The use of ACE inhibitor and/or ARB was relatively low (70%) in the J-SHIFT study (**Table 1**). Although the reasons for this low use of ACE inhibitor and/or ARB were not clear because the information was not available, the effects of ivabradine on the primary composite endpoint were consistent across subgroups with and without ACE inhibitor and/or ARB use (test for interaction P=0.8025) (**Figure 4**). Beta-blockers were used in 95% of patients, but only 20% of patients were on the target dose (**Table 1**). The percentage distribution of doses of β-blockers in the J-SHIFT study was similar to that reported in the SHIFT study (**Supplementary Table 2**). The effects of ivabradine on the primary composite endpoint were consistent across subgroups with different doses of β-blockers (test for interaction P=0.9076) (**Figure 4**). Moreover, mean daily doses of carvedilol of 9.8 mg and bisoprolol of 3.1 mg in the J-SHIFT study were comparable to those in clinical studies in Japan.[12,13]

Ivabradine reduced the resting HR by 15 beats/min from the baseline value of 82 beats/min and the reduced HR was well maintained throughout the course of the treatment period (**Figure 2A**). This reduction was consistent with the 15 beats/min reported in the SHIFT study.[3] It was consistent also in subgroups, including the primary cause of HF, baseline HR, baseline LVEF, and β-blocker dose (data not shown).

Another important finding of the J-SHIFT study was that ivabradine reversed LV remodeling and improved LVEF (**Figure 5**). Treatment with ivabradine was associated

with a significant reduction in the LVESV index by 16.3 mL/m^2 and a significant increase in LVEF by 11.1%. These results were in line with the decrease in LVESV index (7.0 mL/m^2) and the increase in LVEF (2.4%) reported from the SHIFT echocardiography substudy.[14] However, the extent of these changes was greater in the J-SHIFT study than in the SHIFT substudy.

The primary composite endpoint tended to be lower in patients with greater HR reduction (**Supplementary Figure 4**). In addition, there was a significant relationship between the changes in HR and those in LVEF (**Supplementary Figure 5**). The incidence of the primary composite endpoint was significantly lower in patients with a greater increase in LVEF (**Supplementary Figure 6**). The present study suggested that the LV functional and morphological changes induced by ivabradine might have relationships with HR reduction and prognosis. These positive effects of ivabradine on LV remodeling and prognosis were consistent with previous substudies of the SHIFT study.[8,14]

The changes in the plasma BNP/NT-proBNP levels were not associated with echocardiographic LV functional changes in the J-SHIFT study. There are several explanations for the lack of an effect of ivabradine on BNP/NT-proBNP in this study. First, a great variability in BNP/NT-proBNP levels at baseline might make the comparison between the groups inconclusive, especially when the number of studied patients was as small as in this study. Second, the correlation between BNP/NT-proBNP and LVEF has been reported to be relatively weak.[15] Third, the association between LV remodeling and natriuretic peptides has been reported to be unclear under treatment with β-blocker, in contract to that with ACE inhibitor.[16] In fact, similar to our findings, the echocardiographic substudy of the BEAUTIFUL study in patients with coronary artery disease and LV dysfunction also reported that ivabradine did not have significant effects on NT-proBNP levels.[17]

Ivabradine was well tolerated by Japanese patients (**Table 3**). In the SHIFT study, visual side effects such as phosphenes, which are related to HCN inhibition in retina,[18] symptomatic or asymptomatic bradycardia, and atrial fibrillation occurred more frequently in the ivabradine group compared with the placebo group.[3] In the J-SHIFT study, the incidences of these AEs were comparable between the groups (**Table 3**). Notably, asymptomatic bradycardia occurred in 1 patient (0.8%) in the ivabradine group, but this patient did not need to discontinue treatment, which is especially important considering that 95% of patients had β-blocker therapy. Mild phosphenes were observed in 8 patients (6.3%) in the ivabradine group and this incidence was lower than that reported from the Japanese phase II trial (9.5%), but was higher than in the SHIFT study (3%). None of the patients discontinued treatment.

Study Limitations

There are several potential limitations to be acknowledged. First, the sample size of the J-SHIFT study was too small to evaluate clinical events with statistical significance. However, the sample size was considered suitable for evaluating the consistency of efficacy by ivabradine with that in the SHIFT study. Second, the J-SHIFT study excluded patients with persistent atrial fibrillation or flutter and the results can only be applied to patients with resting HR ≥75 beats/min and sinus rhythm. Third, the background medical treatment for HFrEF in the J-SHIFT study, especially for ACE inhibitor or ARB and β-blocker, was not sufficient based on the Japanese guideline recommendations.[6,7] Therefore, it is unclear whether the efficacy of ivabradine would be similar if more patients were treated by ACE inhibitor or ARB and on the target dose of β-blocker. However, the subgroup analysis of the J-SHIFT study demonstrated that the efficacy of ivabradine was consistent irrespective of the background treatments, as in the SHIFT study (**Figure 4**).

In conclusion, ivabradine had efficacy and safety in Japanese patients with HFrEF, consistent with the SHIFT study.

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Disclosures

This trial was designed and performed by the sponsor, Ono Pharmaceutical Co., Ltd. The data were collected and analyzed, and the first draft manuscript was written by the sponsor. It was fully reviewed and revised by the authors.

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Supplementary Files

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