Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Heart Failure

Heart Rate Control With I_f Inhibitor, Ivabradine, in Japanese Patients With Chronic Heart Failure

– A Randomized, Double-Blind, Placebo-Controlled Phase II Study –

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Background: Elevated heart rate (HR) is an independent risk factor for cardiovascular outcomes in various cardiac diseases, including heart failure (HF).

Methods and Results: Randomized placebo-controlled study was conducted to evaluate the effects of ivabradine, an I_f inhibitor, on the resting HR in 126 Japanese symptomatic HF patients with left ventricular ejection fraction ≤35%, resting HR ≥75 beats/min in sinus rhythm, and stable, optimal background treatment. Patients were randomly allocated into 3 groups: placebo; starting dose of ivabradine 2.5 mg twice daily (BID; 2.5 mg group); 5 mg BID group. The dose was increased up to 7.5 mg BID according to dose-adjustment criteria. After the 6-week treatment, the reductions in resting HR were significant in both the 2.5-mg (16.6±8.1 beats/min) and 5-mg (16.4±9.6 beats/min) groups ($P<0.0001$ for both groups) compared with placebo (1.7±8.7 beats/min). The most frequent side effect of ivabradine was phosphenes, but all were mild. Treatment was discontinued in 1 patient due to HF in the 5 mg group.

Conclusions: Ivabradine starting at 2.5 or 5 mg BID effectively reduced resting HR in Japanese HF patients. Ivabradine at the starting dose of 2.5 mg BID could be safer than 5 mg BID. (*Circ J* 2016; **80:** 668–676)

Key Words: Chronic heart failure; Double-blind placebo-controlled trial; I_f inhibitor; Left ventricular ejection fraction; Resting heart rate

Elevated heart rate (HR) is an independent risk factor for cardiovascular outcomes in various heart diseases, including heart failure (HF).[1,2] There are many hypothetical mechanisms through which elevated HR might directly affect cardiovascular risk, mostly related to increased myocardial oxygen demand,[3] energy depletion,[4] accelerated atherosclerosis,[5] and increased risk of plaque rupture.[6] Beta-blockers have been proved to reduce morbidity and mortality in patients with HF and reduced left ventricular ejection fraction (LVEF)[7–9] and are recommended as the first-line drug. They have numerous actions on the heart, including a decrease in myocardial contractility, blood pressure (BP) and HR, and anti-arrhythmic effects. Among them, the lowering effect of β-blockers on HR may contribute to the improvement in long-term outcomes. A meta-analysis for the efficacy of β-blockers in chronic HF demonstrated that a reduction in HR by 5 beats/min decreased the risk of death by 18%.[10] However, the use of β-blockers remains suboptimal in patients with HF, because of their

Received October 19, 2015; revised manuscript received November 30, 2015; accepted December 1, 2015; released online January 14, 2016 Time for primary review: 10 days

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The Guest Editor for this article was Hiroshi Ito, MD.

Clinical Trial Registration: JapicCTI-132346 (http://www.clinicaltrials.jp/user/cteSearch.jsp)

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ISSN-1346-9843 doi:10.1253/circj.CJ-15-1112

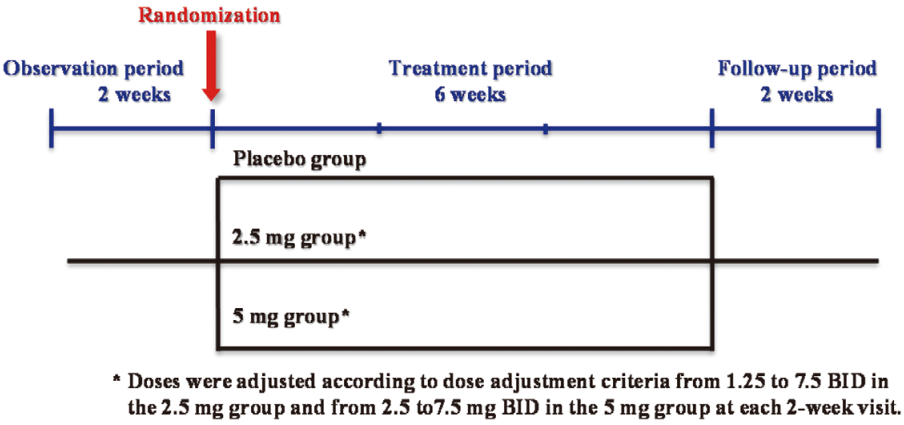

Figure 1. Study design consisted of a 2-week observation period, 6-week treatment period, and 2-week follow-up period without study treatment. Patients who met the entry criteria were randomized into the placebo, 2.5-mg, or 5-mg groups at 1:1:1. The dosage was adjusted according to dose-adjustment criteria at each 2-week visit during the treatment period.

contraindications and side effects.[11]

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Ivabradine is a specific inhibitor of the I_f current in the sinoatrial node, and its oral administration can selectively reduce HR without affecting cardiac conductivity, contractility, repolarization or BP.[12,13] In the SHIFT study, a randomized placebo-controlled trial in 6,505 patients with HF, LVEF ≤35%, and resting HR ≥70 beats/min under stable, optimal conventional therapy, ivabradine significantly decreased HR and reduced the risk of cardiovascular death or hospitalization for worsening HF by 18% compared with placebo.[14] It also reduced the risk of rehospitalization for worsening HF,[15] and improved LV remodeling and quality of life.[16,17] A subgroup analysis demonstrated that ivabradine improved various efficacy endpoints, including all-cause mortality and cardiovascular mortality, in patients with resting HR ≥75 beats/min, which led to its approval in Europe for treatment of patients with resting HR ≥75 beats/min.[18] In addition, ivabradine was effective, irrespective of the dose and type of β-blocker,[19,20] for patients with severe chronic HF (LVEF ≤20% and/or New York Heart Association [NYHA] functional class IV),[21] chronic obstructive pulmonary disease,[22] renal dysfunction (estimated glomerular filtration rate <60 ml/min/1.73 m^2),[23] left bundle branch block,[24] higher age,[25] or low BP.[26]

The SHIFT study included Asian patients, but not Japanese patients. Therefore, efficacy and safety have not been confirmed in these patients. Specifically, in the SHIFT study, the starting dose of ivabradine was 5 mg twice daily (BID) and the dose was adjusted in the range of 2.5, 5, or 7.5 mg BID depending on HR and tolerability. In Japan, the lower starting dose of 2.5 mg BID may need to be evaluated. Therefore, the purpose of this study was to examine the efficacy, focusing on the reduction in resting HR, and safety of ivabradine in Japanese patients with HF and reduced LVEF.

Methods

Study Design and Patients

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial in patients with HF and reduced LVEF. The study was carried out between December 2013 and February 2015 in 73 institutions in Japan. Eligible patients were Japanese men and women who met the following criteria: age ≥20 years, resting HR ≥75 beats/min in sinus rhythm, stable symptomatic chronic HF of NYHA functional class II or higher, LVEF ≤35%, and under optimal, stable treatment according to the Japanese Guideline for Treatment of Chronic Heart Failure (JCS 2010).[27]

The main exclusion criteria were congenital heart disease; myocardial infarction within 2 months; persistent atrial fibrillation or atrial flutter; sick sinus syndrome; sinoatrial node block or 2nd- or 3rd-degree atrioventricular block; atrioventricular pacing operative for ≥40% of the day or with backup pacing rate ≥60 beats/min; severe or uncontrolled hypertension or symptomatic hypotension; moderate or severe hepatic disease; severe renal disease; and anemia. Medications including non-dihydropyridine calcium-channel blockers, class I antiarrhythmics, and moderate or strong inhibitors of cytochrome P450 3A4 were not allowed at the inclusion or during the study.

The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the ethical committee or review board of each institution. All patients provided written consent before randomization.

Randomization and Masking

After an observation period of 2 weeks to enable confirmation of the inclusion and exclusion criteria, patients were randomly allocated to 3 treatment groups: placebo group; starting dose of ivabradine 2.5 mg BID (2.5 mg group); 5 mg BID (5 mg group) at 1:1:1. A dynamic allocation method by resting HR and the dose of β-blocker was used to balance the baseline covariates. The patients and investigators were masked to the treatment allocation. All the study drugs (ivabradine (1.25, 2.5, 5 and 7.5 mg) and placebo) were tablets of the same color and size, which was confirmed before the start of the study.

Procedure

As depicted in Figure 1, the study consisted of a 2-week observation period, 6-week treatment period, and 2-week follow-up

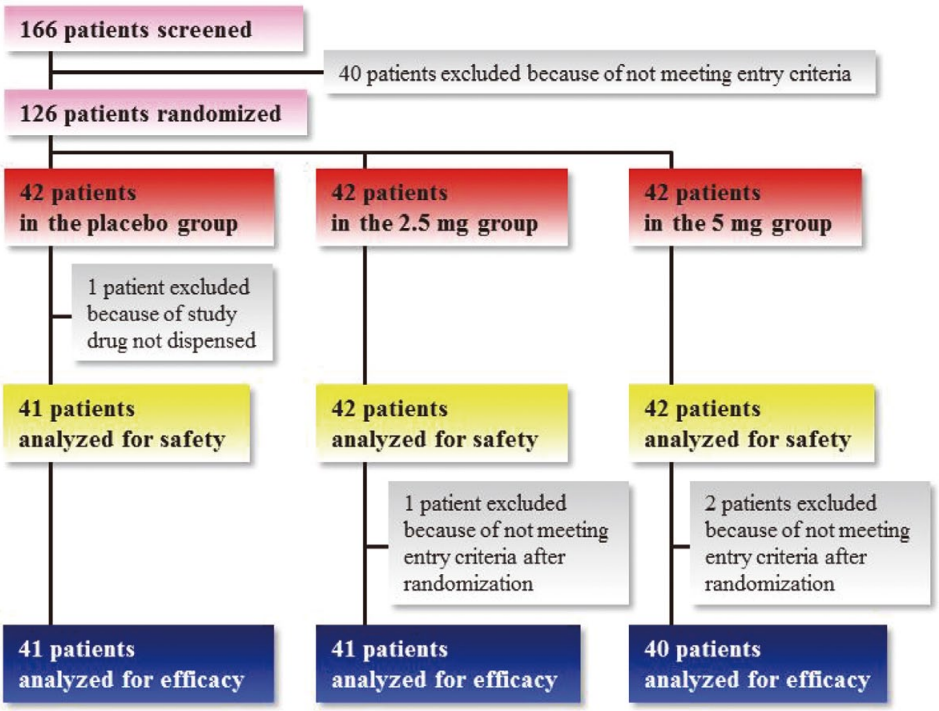


Figure 2. Study patient flow. Screened patients entered the 2-week observation period for confirmation of the inclusion or exclusion criteria.

period without study drug treatment. During the treatment period, the starting dose was 2.5 or 5 mg BID of ivabradine or matching placebo. The dose was adjusted at each 2-week visit in the range of 1.25–7.5 mg BID in the 2.5 mg group and 2.5–7.5 mg BID in the 5 mg group according to the 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 the patient 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 with the lowest dose. All patients were followed until 2 weeks after the treatment.

Efficacy

The primary endpoint was the reduction in resting HR from baseline at the 6-week treatment. The secondary endpoints were change in NYHA functional class, LVEF, and concentrations of plasma B-type natriuretic peptide (BNP), and N-terminal fragment of pro-BNP (NT-proBNP) from baseline. All HRs were analyzed in a central laboratory based on the 12-lead electrocardiogram (ECG) data. BNP and NT-proBNP were also measured in a central laboratory.

Safety

All adverse events (AEs) were recorded during the treatment and follow-up periods. The 12-lead ECG, vital signs including pulse rate, systolic BP (SBP), diastolic BP (DBP), and respiratory rate, and laboratory tests including hematological, biochemical, and urine tests were measured at each visit.

Statistical Analysis

SAS 9.3 software (SAS Institute Inc, Cary, NC, USA) was used for all analyses. Differences in the reduction in resting HR between the ivabradine groups and the placebo group were analyzed by the Dunnett-Hsu method[28] at 6 weeks and analysis of covariance (ANCOVA) at the other time points. NYHA functional class and the changes in BNP and NT-proBNP at 6 weeks from baseline were analyzed by Wilcoxon rank-sum test. SBP and DBP at 6 weeks from baseline were analyzed using t-test. Other parameters were tested by chi-square test for categorical variables and analysis of variance (ANOVA) for continuous variables.

Based on the assumption that the differences in the least mean square of the reductions in resting HR between ivabradine and placebo would be 11.8 and that the standard deviation would be 12.0 for both the 2.5 and 5 mg groups according to the SHIFT study subgroup of resting HR ≥75 beats/min,[18] the estimated number of patients required for the present study was 40 per group (120 patients in total) using the Dunnett-Hsu method (two-tailed) with α=5% and power of test at 95%.

Results

The study patient flow is shown in Figure 2. The 126 study patients were randomly assigned to 3 treatment groups (42 patients per group). Of these, 1 patient in the placebo group was excluded because the study drug was not dispensed, and the remaining 125 patients were analyzed for safety. Of them, 3 patients (1 in the 2.5 mg group and 2 in the 5 mg group) were excluded for violation of the major inclusion criteria, and the remaining 122 patients were analyzed for efficacy.

Table 1 summarizes the baseline characteristics of the patients in the placebo and ivabradine groups. The mean age was 59.0±13.1 years, and 108 (85.7%) patients were male.

Table 1. Baseline Characteristics of the Study Patients

	Placebo (n=42)	Ivabradine		P value*
		2.5-mg group (n=42)	5-mg group (n=42)	
Age (years)	59.4±12.7	57.7±13.0	60.0±13.9	0.7009
Sex (male)	34 (81.0%)	37 (88.1%)	37 (88.1%)	0.5580
BMI (kg/m^2)	24.3±4.3	25.8±5.7	24.6±4.6	0.3526
Cause of HF				
Ischemic	19 (45.2%)	15 (35.7%)	20 (47.6%)	0.5063
Non-ischemic	23 (54.8%)	27 (64.3%)	22 (52.4%)	
Medical history				
Hypertension	21 (50.0%)	20 (47.6%)	23 (54.8%)	0.8007
Myocardial infarction	14 (33.3%)	12 (28.6%)	12 (28.6%)	0.8601
Diabetes	17 (40.5%)	24 (57.1%)	22 (52.4%)	0.2899
Atrial fibrillation or flutter	4 (9.5%)	5 (11.9%)	0	0.0810
NYHA functional class				
II	38 (92.7%)	38 (90.5%)	39 (92.9%)	0.9047
III	3 (7.3%)	4 (9.5%)	3 (7.1%)	
IV	0	0	0	
LVEF (%)	28.5±4.9	28.3±5.6	28.4±4.9	0.9685
Resting heart rate (beats/min)	81.5±7.4	83.2±6.5	83.4±8.2	0.4468
Blood pressure				
Systolic (mmHg)	113.2±16.9	121.7±21.2	119.5±16.2	0.0961
Diastolic (mmHg)	70.3±10.4	73.0±12.4	72.5±12.1	0.5593
BNP (pg/ml)	188.4±189.6	178.3±149.5	252.0±346.3	0.3331
NT-proBNP (pg/ml)	1,134.9±1,506.7	1,103.6±958.8	1,638.4±2,624.2	0.3297
Medications				
ACEI	16 (38.1%)	20 (47.6%)	21 (50.0%)	0.5103
ARB	14 (33.3%)	10 (23.8%)	8 (19.0%)	0.3095
ACEI or ARB	30 (71.4%)	30 (71.4%)	29 (69.0%)	0.9625
β-blocker**	39 (92.9%)	39 (92.9%)	39 (92.9%)	1.0000
MRA	22 (52.4%)	27 (64.3%)	19 (45.2%)	0.2090
Diuretic	32 (76.2%)	36 (85.7%)	35 (83.3%)	0.5009
Digitalis	0	4 (9.5%)	4 (9.5%)	0.1182
Dose of β-blocker				
0% of target dose**	3 (7.1%)	3 (7.1%)	3 (7.1%)	0.9654
0–<50% of target dose	14 (33.3%)	14 (33.3%)	15 (35.7%)	
50–<100% of target dose	13 (31.0%)	9 (21.4%)	11 (26.2%)	
100% of target dose	12 (28.6%)	16 (38.1%)	13 (31.0%)	
Devices				
CRT	2 (4.8%)	6 (14.3%)	0	0.0238
ICD	1 (2.4%)	0	1 (2.4%)	0.6017

Data are shown as n (%) or mean±SD. *Chi-square test for categorical variables and analysis of variance for continuous variables: not significant, P≥0.05 (two-sided test). **For patients receiving carvedilol or bisoprolol; target daily dose 20 mg/day for carvedilol and 5 mg/day for bisoprolol. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BID, twice daily; BMI, body mass index; BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; HF, heart failure; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal fragment of pro-BNP.

The resting HR was 82.7±7.4 beats/min and the LVEF was 28.4±5.1%. The cause of HF was ischemic in 54 (42.9%) patients. Over 90% of patients were in NYHA functional class II, and the rest were class III. An angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker was used in 89 (70.6%) patients, and a β-blocker in 117 (92.9%) patients. Of the 117 patients having a β-blocker, 74 (63.3%) were treated with at least 50% of the target doses defined by the guideline,[28] and 41 (35.0%) were at the target doses. The major reasons for patients not receiving β-blocker therapy or being below target doses were hypotension and dizziness. There were no significant differences in the baseline characteristics of the 3 groups of patients.

The distribution of the final dose of ivabradine demonstrated that the majority of patients (73.8% in the 2.5-mg and 84.6% in the 5-mg group) were on the highest dose of 7.5 mg BID at 6 weeks (**Figure 3**). The final mean doses at 6 weeks were similar between the 2.5-mg and 5-mg groups (6.5±1.8 mg BID vs. 7.1±1.1 mg BID, P=0.4160).

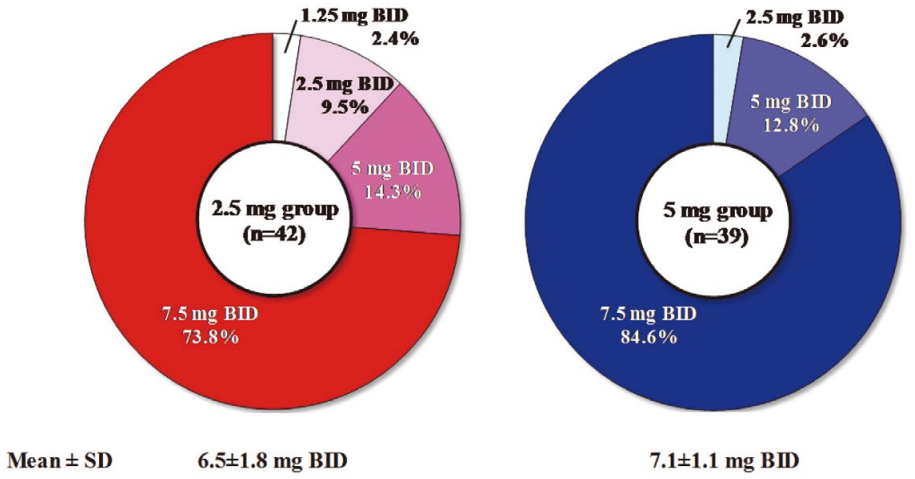
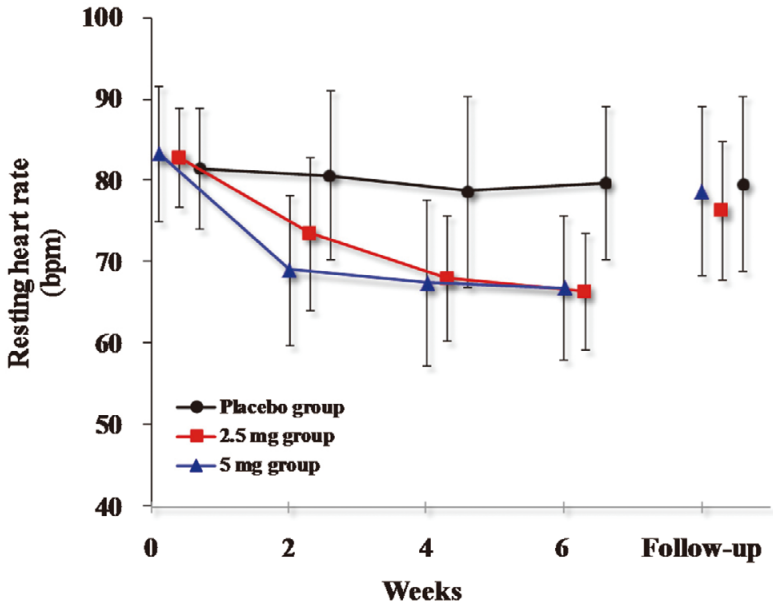


Figure 3. Distribution of the final dose of ivabradine in the 2.5-mg and 5-mg groups. BID, twice daily.



Resting heart rate (bpm)	Placebo group (n=41)	Ivabradine	
		2.5 mg group (n=41)	5 mg group (n=40)
At baseline	81.5 ± 7.4	82.8 ± 6.1	83.3 ± 8.4
At 6 weeks	79.8 ± 9.4	66.4 ± 7.2	66.8 ± 8.8
Change from baseline	-1.7 ± 8.7	-16.6 ± 8.1	-16.4 ± 9.6
Difference from placebo	-	-14.9 ± 8.4	-14.7 ± 9.1
P-value (vs baseline)*	0.0759	<0.0001	<0.0001
P-value (vs placebo group)**	-	<0.0001	<0.0001
P-value (vs 2.5 mg group)*	-	-	0.8276

Figure 4. Change in resting heart rate in the placebo, 2.5-mg, and 5-mg groups during the 6-week treatment period and at the time of 2-week follow-up. Data are shown as mean±SD. The resting heart rate in the follow-up period was measured at 2 weeks after treatment completion or discontinuation. *ANCOVA: not significant, P≥0.05 (two-sided test). **Dunnett-Hsu method: not significant, P≥0.05 (two-tailed test). bpm, beats/min.

Table 2. Resting Heart Rates According to the Final Dose of Ivabradine

Final dose	n	Resting heart rate (beats/min)		
		At baseline	At 6 weeks	Change
1.25 mg BID	1	84	81	–3
2.5 mg BID	5	81.2±7.0	66.0±9.0	–15.2±7.8
5 mg BID	11	77.6±2.8	62.0±4.7	–15.4±5.5
7.5 mg BID	62	84.0±7.5	67.1±8.0	–17.0±9.2

Data are shown as number of patients or mean±SD. BID, twice daily.

Table 3. Secondary Endpoints in Study of Ivabradine in Japanese HF Patients

	Placebo group (n=41)	Ivabradine	
		2.5-mg group (n=41)	5-mg group (n=40)
LVEF (%)			
At baseline	28.5±4.9	28.4±5.6	28.6±4.8
At 6 weeks	31.0±8.8	33.8±8.7	35.0±10.4
Change	2.5±6.0	5.4±7.0	6.4±9.9
P-value (vs. baseline)*	0.0114	<0.0001	0.0003
P-value (vs. placebo)*	–	0.0472	0.0359
P-value (vs. 2.5-mg group)*	–	–	0.6035
BNP (pg/ml)			
At baseline	188.4±189.6	181.3±150.1	239.2±349.7
At 6 weeks	184.2±208.3	181.7±210.0	277.8±318.5
Change	–4.2±56.6	2.6±124.6	40.0±192.8
P-value (vs. baseline)**	0.4709	0.8742	0.0105
P-value (vs. placebo)**	–	0.7055	0.0040
P-value (vs. 2.5-mg group)**	–	–	0.0519
NT-proBNP (pg/ml)			
At baseline	1,134.9±1,506.7	1,124.3±961.2	1,539.0±2,649.7
At 6 weeks	1,148.5±1,650.2	1,006.1±1,120.5	1,656.5±2,842.5
Change	13.7±363.6	–118.2±688.4	64.8±1,091.7
P-value (vs. baseline)**	0.2174	0.1836	0.0634
P-value (vs. placebo)**	–	0.5718	0.0227
P-value (vs. 2.5-mg group)**	–	–	0.0204

Data are shown as mean±SD. *t-test; not significant, P≥0.05 (two-sided test). **Wilcoxon rank-sum test; not significant, P≥0.05 (two-sided test). Abbreviations as in Table 1.

Efficacy

Resting HR decreased from 81.5±7.4 beats/min at baseline to 79.8±9.4 beats/min at 6 weeks (vs. baseline, P=0.0759) in the placebo group, from 82.8±6.1 beats/min to 66.4±7.2 beats/min (vs. baseline, P<0.0001) in the 2.5-mg group, and from 83.3±8.4 beats/min to 66.8±8.8 beats/min (vs. baseline, P<0.0001) in the 5-mg group (**Figure 4**). The reduction in resting HR at 6 weeks from baseline (ie, the primary endpoint) was 16.6±8.1 beats/min in the 2.5-mg group, and 16.4±9.6 beats/min in the 5-mg group, both of which were significantly (P<0.0001 for both groups) greater than in the placebo group (1.7±8.7 beats/min). During the treatment period, the reductions in resting HR were significantly greater in both ivabradine groups than in the placebo group. At 2 weeks, the reduction was greater in the 5-mg group than in the 2.5-mg group (13.6±7.8 beats/min vs. 9.3±9.6 beats/min, P<0.0001). However, it did not differ between the ivabradine groups at the other time points during the treatment period. At the end of the follow-up period, the resting HRs were similar among the 3 groups and returned to the baseline level.

Resting HR at 6 weeks did not differ according to the final doses of ivabradine and its reduction was also similar among the final ivabradine doses of 2.5, 5, and 7.5 mg BID at 6 weeks (**Table 2**).

Table 3 summarizes the secondary endpoints. The increase in LVEF by ivabradine was 5.4±7.0% in the 2.5-mg group and 6.4±9.9% in the 5-mg group, both of which were statistically significant (P=0.0472 and 0.0359, respectively) compared with the placebo group (2.5±6.0%). Both the plasma BNP and NT-proBNP levels in the 5-mg group significantly increased compared with the placebo or 2.5-mg group. NYHA functional class did not change (data not shown).

Safety

Table 4 summarizes the AEs with an incidence ≥5% observed in any of the groups. The incidence of AEs was 54.8% in the 2.5-mg group and 64.3% in the 5-mg group, which was significantly higher than in the placebo group (29.3%). The most frequent AE was phosphenes (2.4% in placebo group, 9.5% in the 2.5-mg group and 21.4% in the 5-mg group, P=0.0213). In 6 of 9 cases of phosphenes in the 5-mg group, the AE occurred with the initial dose, but no cases of phosphenes were observed

Table 4. Adverse Events (≥5% in Any Group) in Study of Ivabradine in Japanese HF Patients

Adverse event	Placebo group (n=41)	Ivabradine		P value*
		2.5-mg group (n=42)	5-mg group (n=42)	
All	12 (29.3%)	23 (54.8%)	27 (64.3%)	0.0044
HF	1 (2.4%)	1 (2.4%)	5 (11.9%)	0.0927
Phosphenes	1 (2.4%)	4 (9.5%)	9 (21.4%)	0.0213
Diarrhea	1 (2.4%)	3 (7.1%)	0	0.1675
Nasopharyngitis	2 (4.9%)	2 (4.8%)	10 (23.8%)	0.0064

Data are shown as n (%). *Chi-square test: not significant, P≥0.05 (2-sided test). Abbreviations as in Table 1.

with the initial dose in the 2.5-mg group. Four serious AEs were reported: acute myocardial infarction in 1 patient (2.4%) from the placebo group, and HF in 2 patients (4.8%) and pneumonia in 1 patient (2.4%) from the 5-mg group. One of the HF patient in the 5-mg group discontinued ivabradine. All cases of serious AEs recovered or improved during the study period or after study completion. Bradycardia was not reported in this study. BP in either ivabradine group or placebo group did not change; the change in SBP at 6 weeks from baseline was 1.8±10.7 mmHg (P=0.2951) in the placebo group, −1.7±13.2 mmHg (P=0.4061) in the 2.5-mg group, and 4.1±13.0 mmHg (P=0.0553) in the 5-mg group; the respective change in DBP was 0.4±7.5 mmHg (P=0.7109) in the placebo group, −1.7±9.5 mmHg (P=0.2612) in the 2.5-mg group, and −0.7±11.7 (P=0.6930) in the 5-mg group. There were no apparent changes in laboratory test results or 12-lead ECG.

Discussion

This randomized double-blind placebo-controlled phase II trial evaluated the effects of ivabradine on Japanese chronic HF patients with LVEF ≤35% and resting HR ≥75 beats/min in sinus rhythm using a dose-adjusting procedure. It demonstrated that the reduction in resting HR after 6 weeks of treatment was 16.6 beats/min in the 2.5-mg group and 16.4 beats/min in the 5-mg group, both of which were significantly greater than that in the placebo group (1.7 beats/min).

The degree of reduction in resting HR in this study was comparable to the data from the SHIFT study subgroup (17.5 beats/min at 28 days in the subgroup of baseline resting HR ≥75 beats/min).[18] Compared with the patient characteristics in the SHIFT study, the present study included more patients in NYHA functional class II (90% vs. 50%) and non-ischemic cause of HF (60% vs. 35%). However, there was no significant interaction between the reduction in resting HR and NYHA functional class or the cause of HF (data not shown). Although HR during exercise was not assessed in this study, ivabradine is also reported to reduce HR during exercise and to improve exercise tolerance.[29] In the present study, the reduction in resting HR was similar among the final doses of ivabradine ranging from 2.5 to 7.5 mg BID (15.2–17.0 beats/min). These findings suggest that the range of appropriate dose adjustment for Japanese HF patients is similar to that for non-Japanese patients (ie, 2.5–7.5 mg BID).

LVEF was significantly increased by ivabradine compared with placebo, in agreement with the SHIFT study.[18] On the other hand, both BNP and NT-proBNP in the 5-mg group were significantly increased compared with the placebo or 2.5-mg groups. This study had a short duration of treatment and a small number of patients. Therefore, further study is needed to evaluate the effects of ivabradine on LVEF, BNP and NT-proBNP. NYHA functional class also did not change by ivabradine treatment in our study. In the SHIFT study, ivabradine improved NYHA functional class, even though the improvement was small,[14] so our result might also be attributable to the limitations of our study described above.

All AEs in the present study were similar to those reported previously in the SHIFT study.[14] The incidence of phosphenes was 9.5% (4 of 42 patients) in the 2.5-mg group and 21.4% (9 of 42 patients) in the 5-mg group, which was higher than in the previous study (2.8%).[14] All cases of phosphenes were observed in patients with ivabradine 5 mg BID or higher, and were mild and improved during the study. The reasons for higher incidence of phosphenes are not identified, so further studies with larger numbers of patients and longer duration of treatment are needed to clarify this point. Bradycardia was not reported as an AE in this study; however, the HR in 1 patient decreased to less than 50 beats/min at 2 consecutive visits (40 beats/min at 2 weeks and 45 beats/min at 4 weeks) in the 5-mg group and ivabradine was discontinued at 4 weeks according to the dose-adjustment criteria. HF was reported as an AE in 6 patients from the ivabradine groups (1 from the 2.5-mg group, 5 from the 5-mg group). All these AEs were observed in patients with ivabradine 5 mg BID or higher. Of these, 2 patients needed hospitalization and were judged as serious AE. Nasopharyngitis occurred in 23.8% (10 of 42 patients) of the 5-mg group in the present study. The reason for the higher incidence in nasopharyngitis in this study was not clear. However, all cases of nasopharyngitis were judged to be unrelated to ivabradine by investigators. In addition to the results for BNP and NT-proBNP, based on the safety results, the starting dose of ivabradine 2.5 mg BID should be safer than 5 mg BID for Japanese HF patients.

In conclusion, ivabradine was effective in reducing the resting HR in Japanese patients with chronic HF and improving their LVEF. Although both starting doses of 2.5 mg BID and 5 mg BID were effective, the lower starting dose might be superior for safety and tolerability.

Disclosures (Conflict of Interest)

This trial was designed and performed by the sponsor (Ono Pharmaceutical). 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.

H.T. has received speakers' bureau/honorarium from MSD, Ono Pharmaceutical, Takeda Pharmaceutical, Daiichi-Sankyo, Teijin Pharma, Nippon Boehringer Ingelheim, Bayer Yakuhin, Bristol-Myers Squibb, and research funds from Takeda Pharmaceutical, Bayer Yakuhin, Nippon Boehringer Ingelheim, Tanabe Mitsubishi Pharma, Sanofi, and Daiichi-Sankyo, honorarium for writing promotional material for Medical Review, and consultation fees from Ono Pharmaceutical.

S.M. has received speakers' bureau/honorarium from Tanabe Mitsubishi Pharma, Daiichi-Sankyo, Takeda Pharmaceutical, Ono Pharmaceutical, MSD, Pfizer, Bayer Yakuhin, Nippon Boehringer Ingelheim, Kyowa Hakko Kirin, Toa Eiyo, Actelion Pharmaceuticals Japan, Philips Respironics GK, Teijin Pharma, Medtronic Japan, St. Jude Medical, Boston Scientific Japan, and Torii Pharmaceutical, honorarium for writing promotional

material for Medtronic Japan, Teijin Pharma, Kyowa Hakko Kirin, research funds from Tanabe Mitsubishi Pharma, Daiichi-Sankyo, Takeda Pharmaceutical, Ono Pharmaceutical, MSD, Pfizer, Kyowa Hakko Kirin, Toa Eiyo, Actelion Pharmaceuticals Japan, Teijin Pharma, Medtronic Japan, St. Jude Medical, Abbott Japan, Nippon Boehringer Ingelheim, and Bayer Yakuhin, and consultation fees from Ono Pharmaceutical.

A.Y. has received speakers' bureau/honorarium from Nippon Boehringer Ingelheim, Toa Eiyo, Tanabe Mitsubishi Pharma, and Daiichi-Sankyo, research funds from Omron healthcare, scholarship funds from Omron healthcare, FUJIFILM RI Pharma, Astra Zeneca, Astellas Pharma, Nihon Medi-Physics, Bayer Yakuhin, Pfizer, Sumitomo Dainippon Pharma, MSD, Daiichi-Sankyo, Nippon Boehringer Ingelheim, Takeda Pharmaceutical, Mochida Pharmaceutical, Tanabe Mitsubishi Pharma, and Kyowa Hakko Kirin, consultation fees from Ono Pharmaceutical, and is affiliated with endowed departments sponsored by Medtronic Japan.

H.O. has received speakers' bureau/honorarium from Astra Zeneca, MSD, Sanofi, Daiichi-Sankyo, Takeda Pharmaceutical, Tanabe Mitsubishi Pharma, Teijin Pharma, Nippon Boehringer Ingelheim, Bayer Yakuhin, Pfizer, and Bristol-Myers Squibb, research funds from MSD, ITI, Astellas Pharma, Abbott Vascular Japan, Itamar Medical Japan, Eisai, Otsuka Pharmaceutical, Ono Pharmaceutical, Kaneka Medics, Kyowa Hakko Kirin, Sanofi, GM medical, Genzyme Japan, Johnson & Johnson, St. Jude Medical, Daiichi-Sankyo, Sumitomo Dainippon Pharma, Takeda Pharmaceutical, Tanabe Mitsubishi Pharma, Chugai Pharmaceutical, Teijin Pharma, Terumo, Nihon Kohden, Nippon Boehringer Ingelheim, Medtronic Japan, Japan Lifeline, Bayer Yakuhin, BIOTRONIK Japan, Pfizer, Fides-one, Fukuda Denshi, Bristol-Myers Squibb, Boston Scientific Japan, and Mochida Pharmaceutical, and consultation fees from Ono Pharmaceutical.

H.S. has received speakers' bureau/honorarium from Daiichi-Sankyo, Bayer Yakuhin, Kyowa Hakko Kirin, and Nippon Boehringer Ingelheim, research funds from Bayer Yakuhin, Asahi Kasei Pharma, MSD, Kowa Pharmaceutical, Teijin Pharma, Tanabe Mitsubishi Pharma, Takeda Pharmaceutical, Daiichi-Sankyo, Bristol-Myers Squibb, Mochida Pharmaceutical, FUJIFILM RI Pharma, Sumitomo Dainippon Pharma, Eisai, Shionogi, Pfizer, Nippon Shinyaku, Otsuka Pharmaceutical, Sanofi, Ono Pharmaceutical, Sanwa Kagaku Kenkyusho, BIOTRONIK Japan, TESCO, and Abbott Vascular Japan, consultation fees from Ono Pharmaceutical, and is affiliated with endowed departments sponsored by Astra Zeneca, Kyowa Hakko Kirin, Nippon Boehringer Ingelheim, Sumitomo Dainippon Pharma, Novartis Pharma, Bayer Yakuhin, Daiichi-Sankyo, Medtronic Japan, Asahi Kasei Pharma, TESCO, Terumo, St. Jude Medical, Nihon Kohden, and Hitachi Aloka Medical.

Y. Kihara has received speakers' bureau/honorarium from Takeda Pharmaceutical, Bayer Yakuhin, Medtronic Japan, Teijin Pharma, and Nippon Boehringer Ingelheim, research funds from Daiichi-Sankyo and Takeda Pharmaceutical, and consultation fees from Ono Pharmaceutical.

Y.S. has received research funds from Tanabe Mitsubishi Pharma, Shionogi, Daiichi-Sankyo, Takeda Pharmaceutical, and Otsuka Pharmaceutical, Baxter, consultation fees from Ono Pharmaceutical, and is affiliated with endowed departments sponsored by MSD.

N.H. has received research funds from Nippon Boehringer Ingelheim, Daiichi-Sankyo, Takeda Pharmaceutical, and consultation fees from Ono Pharmaceutical.

H.I. has received speakers' bureau/honorarium from Takeda Pharmaceutical, Daiichi-Sankyo, MSD, Mochida Pharmaceutical, Tanabe Mitsubishi Pharma, Kowa Pharmaceutical, Toa Eiyo, Otsuka Pharmaceutical, Medtronic Japan, Astellas Pharma, Bayer Yakuhin, and Ono Pharmaceutical, research funds from Takeda Pharmaceutical, Daiichi-Sankyo, MSD, Mochida Pharmaceutical, Tanabe Mitsubishi Pharma, Kowa Pharmaceutical, Toa Eiyo, Otsuka Pharmaceutical, Medtronic Japan, Astellas Pharma, Bayer Yakuhin, Shionogi, Sumitomo Dainippon Pharma, and Ono Pharmaceutical, honorarium for writing promotional material for Daiichi-Sankyo, consultation fees from Ono Pharmaceutical, and is affiliated with an endowed department sponsored by Medtronic Japan.

J.A. has received speakers' bureau/honorarium from Actelion, Sanofi, Tanabe Mitsubishi Pharma, Takeda Pharmaceutical, Mochida Pharmaceutical, Shionogi, Kaneka, Astra Zeneca, Astellas Pharma, Volcano, Terumo, Eisai, Bristol-Myers Squibb, St. Jude Medical, Kyowa Hakko Kirin, Pfizer, Ono Pharmaceutical, Abbott Vascular Japan, Toa Eiyo, JIMRO, Kissei, and Sumitomo Dainippon Pharma, scholarship funds from Kissei, Astellas Pharma, Mediphysics, Ono Pharmaceutical, Bristol-Myers Squibb, Pfizer, Behringer Ingelheim, Kyowa Hakko Kirin, Bayer, Daiichi-Sankyo, Eisai, Teijin, Kowa, Pharmaceutical, Mochida Pharmaceutical, Abbott Vascular Japan, Medtronic Japan, Asahi Intec, Astra Zeneca, Sumitomo Dainippon Pharma, Otsuka Pharmaceutical, Tanabe Mitsubishi Pharma, Takeda Pharmaceutical, and Japan Lifeline, and consultant fees from Ono Pharmaceutical.

T.I. has received speakers' bureau/honorarium from Otsuka Pharmaceutical, Daiichi-Sankyo, Medtronic Japan, and consultation fees from Ono Pharmaceutical.

T.T. and Y. Kawasaki are employees of Ono Pharmaceutical.

Acknowledgments

We thank the following physicians who participated as investigators in this study and who made this study possible: Hironori Murakami (Department of Cardiovascular Medicine, Teine Keijinkai Hospital); Yoshiaki Katahira (Cardiovascular Center, Tohoku Pharmaceutical University Hospital); Tsuyoshi Shinozaki (Department of Cardiovascular Medicine, National Hospital Organization, Sendai Medical Center); Masahiro Yagi (Department of Cardiology, Sendai Cardiovascular Center); Syouji Suzuki (Department of Cardiology, Kasumigaura Medical Center); Kazuomi Kario (Cardiovascular Medicine, Jichi Medical University); Noriaki Takama (Department of Cardiovascular Medicine, Gunma University Hospital); Shigeyuki Nishimura (Department of Cardiology, Saitama Medical University International Medical Center); Yoshihiko Seino (Department of Cardiology, Nippon Medical School Chiba-Hokusoh Hospital); Atsushi Hirayama (Department of Cardiovascular Medicine, Nihon University Itabashi Hospital); Seiji Fukamizu (Department of Cardiology, Tokyo Metropolitan Hiroo Hospital); Tsuyoshi Shiga (Department of Cardiology, Tokyo Women's Medical University Hospital); Keiichi Fukuda (Department of Cardiology, Keio University School of Medicine); Yoshifumi Takata (Department of Cardiology, Tokyo Medical University); Hiroyuki Niinuma (Department of Cardiology, St Lukes International Hospital); Kouichi Fuse (Department of Cardiology, Tachikawa General Hospital); Haruyuki Taguchi (Department of Medicine, Cardiovascular Division, Osaka Ekisaikai Hospital); Tadaaki Kamitani (Department of Cardiology, Matsushita Memorial Hospital); Tohru Masuyama (Cardiovascular Division, Department of Internal Medicine, Hyogo College of Medicine); Yutaka Furukawa (Department of Cardiology, Kobe City Medical Center, General Hospital); Yorihiko Higashino (Department of Cardiology, Higashi Takarazuka Satoh Hospital); Akira Yamada (Department of Cardiology, Aso Iizuka Hospital); Hideki Shimomura (Department of Cardiology, Fukuoka Tokushukai Hospital); Toshiaki Kadokami (Department of Cardiovascular Medicine, Saiseikai Futsukaichi Hospital); Tatsuya Nunohiro (Department of Cardiovascular Medicine, Nagasaki Harbor Medical Center City Hospital); Hitoshi Nakashima (Department of Cardiology, National Hospital Organization Kagoshima Medical Center); Yoshihiro Morino (Division of Cardiology, Department of Internal Medicine, Iwate Medical University Hospital); Wataru Shimizu (Department of Cardiovascular Medicine, Nippon Medical School Hospital); Kazuki Fukui (Department of Cardiology, Kanagawa Cardiovascular and Respiratory Center); Kaoru Okishige (Department of Cardiology, Yokohama City Minato Red Cross Hospital); Masayuki Takamura (Department of Cardiology, Kanazawa University Hospital); Toshikazu Tanaka (Department of Cardiology, Okazaki City Hospital); Kan Zen (Department of Cardiology, Omihachiman Community Medical Center); Atsuyuki Wada (Division of Cardiology, Kusatsu General Hospital); Toshihisa Anzai (Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center); Shinobu Hosokawa (Department of Cardiology, Tokushima Red Cross Hospital); Jun Suzuki (Department of Cardiology, Pulmonology, Hypertension and Nephrology, Ehime University Hospital); Ryuichi Matsukawa (Department of Cardiology, Saiseikai Fukuoka Hospital); Tomoya Onodera (Department of Cardiology, Shizuoka City Shizuoka Hospital); Takahiro Saeki (Department of Cardiology, Kanazawa Medical Center); Tetsuo Konno (Department of Cardiology, Kanazawa University Hospital); Yukio Ozaki (Department of Cardiology, Fujita Health University Hospital); Koichiro Kuwahara (Department of Cardiovascular Medicine, Kyoto University Hospital); Tetsuya Haruna (Cardiovascular Center, Tazuke Kofukai Medical Research Institute , Kitano Hospital); Yasuhiko Sakata (Department of Cardiovascular Medicine, Tohoku University Hospital); Mitsuaki Isobe (Department of Cardiovascular Medicine, Tokyo Medical and Dental University Hospital); Harumizu Sakurada (Department of Cardiology, Tokyo Metropolitan Health and Medical Treatment Corporation Ohkubo Hospital); Masayoshi Ajioka (Department of Cardiology, Tosei General Hospital); Nobuhiro Nishii (Department of Cardiovascular Medicine, Okayama University Hospital); Atsushi Hirohata (Department of Cardiovascular Medicine, The Sakakibara Heart Institute of Okayama); Megumi Yamamuro (Department of Cardiovascular Medicine, Kumamoto University Hospital); Kazuo Kimura (Cardiovascular Center, Yokohama City University School of Medicine); Tetsuya Sato (Department of Cardiovascular Medicine, Okayama Red Cross General Hospital); Yasushi Sakata (Department of Cardiovascular Medicine, Osaka University Hospital); Yuichi Noguchi (Department of Cardiology, Tsukuba Medical Center Hospital); Koichiro Kinugawa (Department of Cardiology, Tokyo University Hospital); Hideaki Yoshino (Department of Internal Medicine II, Kyorin University Hospital); Takahiro Okumura (Department of Cardiology, Nagoya University Hospital); Takehiko Kuramochi (Department of Cardiology, Chiba Nishi General

Hospital); Yusuke Fujino (Department of Cardiology, New Tokyo Hospital); Akihiko Takahashi (Department of Cardiology, Sakurakai Takahashi Hospital); Nobuhide Miyamoto (Department of Cardiology, Oita Oka Hospital); Kazuhiro Yamamoto (Department of Molecular Medicine and Therapeutics, Tottori University Hospital); Kenji Ando (Department of Cardiology, Kokura Memorial Hospital); Tetsuya Takaishi (Department of Cardiovascular Medicine, Yodogawa Christian Hospital); Ichiro Matsumoto (Cardiovascular Center, Takamatsu Hospital); Shigeru Fukuzawa (Department of Cardiology, Funabashi Municipal Medical Center); Yoshikazu Yazaki (Department of Cardiovascular Medicine, Saku General Hospital); Toshiro Kurosawa (Department of Cardiovascular Medicine, Machida Municipal Hospital). We also thank Takuhiro Yamaguchi (Department of Biostatistics, Tohoku University Graduate School of Medicine) for advice on statistical analysis.

References

1. Kannel WB, Kannel C, Paffenbarger RS Jr, Cupples LA. Heart rate and cardiovascular mortality: The Framingham Study. *Am Heart J* 1987; **113:** 1489–1494.
2. Ushigome R, Sakata Y, Nochioka K, Miyata S, Miura M, Tadaki S, et al. Temporal trends in clinical characteristics, management and prognosis of patients with symptomatic heart failure in Japan: Report from the CHART studies. *Circ J* 2015; **79:** 2396–2407.
3. Panza JA, Diodati JG, Callahan TS, Epstein SE, Quyyumi AA. Role of increases in heart rate in determining the occurrence and frequency of myocardial ischemia during daily life in patients with stable coronary artery disease. *J Am Coll Cardiol* 1992; **20:** 1092–1098.
4. Ingwall JS, Weiss RG. Is the failing heart energy starved?: On using chemical energy to support cardiac function. *Circ Res* 2004; **95:** 135–145.
5. Giannoglou GD, Chatzizisis YS, Zamboulis C, Parcharidis GE, Mikhailidis DP, Louridas GE. Elevated heart rate and atherosclerosis: An overview of the pathogenetic mechanisms. *Int J Cardiol* 2008; **126:** 302–312.
6. Heidland UE, Strauer BE. Left ventricular muscle mass and elevated heart rate are associated with coronary plaque disruption. *Circulation* 2001; **104:** 1477–1482.
7. Colucci WS, Packer M, Bristow MR, Gilbert EM, Cohn JN, Fowler MB, et al. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure: US Carvedilol Heart Failure Study Group. *Circulation* 1996; **94:** 2800–2806.
8. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): A randomised trial. *Lancet* 1999; **353:** 9–13.
9. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in-Congestive Heart Failure (MERIT-HF). *Lancet* 1999; **353:** 2001–2007.
10. McAlister FA, Wiebe N, Ezekowitz JA, Leung AA, Armstrong PW. Meta-analysis: Beta-blocker dose, heart rate reduction, and death in patients with heart failure. *Ann Intern Med* 2009; **150:** 784–794.
11. Komajda M. Current challenges in the management of heart failure. *Circ J* 2015; **79:** 948–953.
12. Sulfi S, Timmis AD. Ivabradine: The first selective sinus node I_f channel inhibitor in the treatment of stable angina. *Int J Clin Pract* 2006; **60:** 222–228.
13. Deedwania P. Selective and specific inhibition of I_f with ivabradine for the treatment of coronary artery disease or heart failure. *Drugs* 2013; **73:** 1569–1586.
14. Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): A randomised placebo-controlled study. *Lancet* 2010; **11:** 875–885.
15. Borer JS, Böhm M, Ford I, Komajda M, Tardif JC, O'Maera E, et al. Effect of ivabradine on recurrent hospitalization for worsening heart failure in patients with chronic systolic heart failure: The SHIFT Study. *Eur Heart J* 2012; **33:** 2813–2820.
16. Tardif JC, O'Maera E, Komajda M, Böhm M, Borer JS, Ford I, et al. Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: Results from the SHIFT echocardiography substudy. *Eur Heart J* 2011; **33:** 2507–2515.
17. Ekman I, Chassany O, Komajda M, Böhm M, Borer JS, Ford I, et al. Heart rate reduction with ivabradine and health related quality of life in patients with chronic heart failure: Results from the SHIFT study. *Eur Heart J* 2011; **32:** 2395–2404.
18. Böhm M, Borer J, Ford I, Gonzalez-Juanatey JR, Komajda M, Lopez-Sendon J, et al. Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: Analysis from the SHIFT study. *Clin Res Cardiol* 2013; **102:** 11–22.
19. Swedberg K, Komajda M, Böhm M, Borer J, Robertson M, Tavazzi L, et al. Effects of outcomes of heart rate reduction by ivabradine in patients with congestive heart failure: Is there an influence of beta-blocker dose? *J Am Coll Cardiol* 2012; **59:** 1938–1945.
20. Bocchi EA, Böhm M, Borer JS, Ford I, Komajda M, Swedberg K, et al. Effect of combining ivabradine and β-blockers: Focus on the use of carvediol in the SHIFT population. *Cardiology* 2015; **131:** 218–224.
21. Borer JS, Böhm M, Ford I, Robertson M, Komajda M, Tavazzi L, et al. Efficacy and safety of ivabradine in patients with severe chronic systolic heart failure (from the SHIFT study). *Am J Cardiol* 2014; **113:** 497–503.
22. Tavazzi L, Swedberg K, Komajda M, Böhm M, Borer JS, Lainscak M, et al. Clinical profiles and outcomes in patients with chronic heart failure and chronic obstructive pulmonary disease: An efficacy and safety analysis of SHIFT study. *Int J Cardiol* 2013; **170:** 182–188.
23. Voors AA, van Veldhuisen DJ, Robertson M, Ford I, Borer JS, Böhm M, et al. The effect of heart rate reduction with ivabradine on renal function in patients with chronic heart failure: An analysis from SHIFT. *Eur J Heart Fail* 2014; **16:** 426–434.
24. Reil JC, Robertson M, Ford I, Borer JS, Komajda M, Swedberg K, et al. Impact of left bundle branch block on heart rate and its relationship to treatment with ivabradine in chronic heart failure. *Eur J Heart Fail* 2013; **15:** 1044–1052.
25. Tavazzi L, Swedberg K, Komajda M, Böhm M, Borer JS, Lainscak M, et al. Efficacy and safety of ivabradine in chronic heart failure across the age spectrum: Insights from the SHIFT study. *Eur J Heart Fail* 2013; **15:** 1296–1303.
26. Komajda M, Böhm M, Borer JS, Robertson M, Manolis AJ, Tavazzi L, et al. Efficacy and safety of ivabradine in patients with chronic systolic heart failure according to blood pressure level in SHIFT. *Eur J Heart Fail* 2014; **16:** 810–816.
27. Matsuzaki M, Ishii M, Izumi T, Ito H, Ito H, Ueda Y, et al. Guidelines for treatment of chronic heart failure (JCS 2010) (updated September 13, 2013). http://www.j-circ.or.jp/guideline/pdf/JCS2010_matsuzaki_h.pdf (accessed October 1, 2015).
28. Hsu JC. The factor analytic approach to simultaneous inference in the general linear model. *J Comput Graph Stat* 1992; **1:** 151–168.
29. Bagriy AE, Schukina EV, Samoilova OV, Pricolota OA, Malovichko SI, Pricolota AV, et al. Addition of ivabradine to β-blocker improves exercise capacity in systolic heart failure patients in a prospective, open-label study. *Adv Ther* 2015; **32:** 108–119.