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Effect of Ivabradine on Left Ventricular Diastolic Function of Patients with Heart Failure with Preserved Ejection Fraction

-IVA-PEF Study-

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Abstract

Background: High resting heart rate (HR) is a known marker of cardiovascular outcomes for heart failure (HF) patients. Ivabradine is a new class of HR lowering drug and a specific inhibitor of the I_f current in the sinoatrial node. Ivabradine substantially and significantly reduces major risks associated with HF when added to guideline-based treatment for left ventricular (LV) ejection fraction ≤35% and HR ≥70 bpm in sinus rhythm. On the other hand, HF with preserved ejection fraction (HFpEF) currently accounts for roughly half of all HF cases and usually presents as LV diastolic dysfunction. However, the association between HR reduction and LV diastolic function for HFpEF patients remains uncertain.

Methods/design: This investigation into the effect of IVAbradine on left ventricular diastolic function of patients with heart failure with Preserved Ejection Fraction (IVA-PEF) is a multicenter, prospective, uncontrolled, open-label, single assignment, and an interventional single-arm study to investigate the effect of ivabradine on LV diastolic function of HFpEF patients. The key inclusion criterion is HFpEF with resting HR ≥75bpm in sinus rhythm. After completed informed consent forms are obtained, patients will be given 5 mg/day of ivabradine during the study. LV diastolic function is assessed in terms of mitral inflow E and mitral e' annular velocities (E/e'). The primary endpoint will be defined as a change in E/e′ between baseline and 3 months after the start of administration of ivabradine.

Conclusion: The findings of our trial may provide a new perspective on Ivabradine for the treatment of HFpEF.

Introduction

Heart failure (HF) is one of the most common cardiovascular disorders [1]. It is estimated that 1 in 5 people will develop HF in their lifetime [2]. Its prevalence is estimated at 2% of the population in western countries and its annual incidence now approaches 5 to 10 per 1,000 persons [3, 4]. In addition, its prevalence is 7% for people 75 to 84 years old and over 10% for those 85 years old and over [5]. Thus, the development of novel therapeutic approaches for the treatment of this disorder is crucial. Although standard pharmacological treatment including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), β-blockers, and mineralocorticoid receptor antagonists (MRA) has substantially improved outcomes [6, 7], the prognosis of HF remains less than gratifying.

High resting heart rate (HR) is a known marker of cardiovascular outcomes for HF patients, especially HF with reduced ejection fraction (HFrEF) [8]. One-beat and 5-beat increases of resting HR increase the risk of cardiovascular death and HF hospitalization of HFrEF patients by 3% and 16% in HFrEF patients, respectively [8]. Furthermore, high resting HR was also found to be associated with increased mortality even in general populations [9]. The efficacy of cornerstone pharmacotherapeutic interventions, such as β-blockers and non-dihydropyridine calcium channel blockers, can be evaluated in terms of reductions in HR. Ivabradine is a new class of HR lowering drug which is a specific inhibitor of the I_f current in the sinoatrial node [10]. Results of studies using healthy hearts suggest that, at concentrations attained during therapeutic use, ivabradine has no effect on other channels in the heart or vascular system. Unlike β-blockers, ivabradine does not modify myocardial contractility and intracardiac conduction, even in patients with impaired systolic function [11]. The Systolic Heart failure treatment with the If inhibitor ivabradine Trial (SHIFT) is the first trial to specifically test the effect of isolated HR reduction by means of ivabradine on outcomes for HFrEF patients. The SHIFT study enrolled 6,558 patients who had symptomatic HF, left ventricular (LV) ejection fraction (LVEF) ≤35%, and HR ≥70 bpm in sinus rhythm, and were randomly assigned to an ivabradine group and a

placebo group with a median follow-up of 22.9 months. Treatment with ivabradine was associated with an average reduction in HR of 15 bpm from a baseline value of 80 bpm, which was largely maintained throughout the course of the study. The relative risk of occurrence of the primary endpoint (cardiovascular death or hospital admission for worsening heart failure) for patients treated with ivabradine decreased by 18% compared with the placebo treatment group. Since these effects were caused mainly by hospital admissions for worsening HF (hazard ratio: 0.74, 95% confidence interval: 0.66-0.83; $p<0.0001$) and deaths due to HF (hazard ratio: 0.74, 95% confidence interval: 0.58-0.94, $p=0.014$), ivabradine substantially and significantly reduced major risks associated with HF when added to guideline-based and evidence-based treatment. In addition, the Japanese SHIFT phase III study (J-SHIFT) was designed to evaluate the consistency of results with those from the SHIFT study [12]. Consistency was predefined as a point estimate of the hazard ratio <1 for the primary composite endpoint of cardiovascular death or hospital admission for worsening HF. Because the eligibility of the patients in J-SHIFT comprised symptomatic HF, LVEF≤35%, and HR≥75bpm in sinus rhythm, treatment with ivabradine improved the risk of the primary composite endpoint of cardiovascular death or hospital admission for worsening HF with a hazard ratio of 0.67, thus confirming that the efficacy was similar to that observed in the SHIFT study.

HF with preserved ejection fraction (HFpEF) currently accounts for roughly half of all HF cases, and its prevalence relative to HFrEF continues to rise at an alarming rate of 1% per year. HFrEF evolved into a distinct therapeutic entity partly because large outcome trials demonstrated the efficacy of neurohumoral inhibition. No similar evolution has occurred in the case of HFpEF, where large trials testing neurohumoral inhibition consistently failed to attain a positive primary outcome [13, 14]. HFpEF usually presents as LV diastolic dysfunction identifiable as the earliest functional alteration in the course of HFpEF[4, 15-17]. However, the association between HR or HR reduction and LV diastolic function for HFpEF patients remains uncertain. Moreover, ivabradine is currently restricted to off-label use for HFpEF patients. We thus designed this multicenter, prospective, uncontrolled,

open-label, single assignment, and an interventional single-arm study to investigate the effect of HR reduction by means of ivabradine on the LV diastolic function of HFpEF patients specified as clinical research in the Japanese context.

Methods

Study Design

This investigation into the effect of IVAbradine on left ventricular diastolic function in patients with heart failure with Preserved Ejection Fraction (IVA-PEF) is a multicenter, prospective, uncontrolled, open-label, single assignment, and an interventional single-arm study to examine the effect of ivabradine on LV diastolic function of HFpEF patients at two institutions in Japan (Kobe University Hospital and Hyogo Prefectural Awaji Medical Center) (Figure 1). The trial was registered with the Japan Registry of Clinical Trials (jRCT) (registration number: jRCTs051200059) and posted information will be updated as needed to reflect the protocol amendments and study progress. The protocol was approved by the local ethics committee of our institution (No.C200006).

Eligible patients will meet the following inclusion criteria: (1) age 20 years or older, (2) HFpEF including Stage A HF with or without administration of cardio-protective drugs such as ACE inhibitors, ARBs, β-blockers, or MRAs, (3) resting HR ≥75bpm and potential for additional administration of ivabradine, (4) sinus rhythm, (5) New York Heart Association (NYHA) functional classification and administration of cardio-protective drugs such as ACE inhibitors, ARBs, β-blockers, or MRAs have been constant for 4 weeks before enrollment, (6) written consent from the individual regarding research participation. Patients will be excluded from enrolment study if they meet any of the following apply: (1) atrial fibrillation, (2) unstable or acute HF, (3) cardiogenic shock, (4) severe hypotension (systolic blood pressure <90mmHg or diastolic blood pressure <50mmHg), (5) sick sinus syndrome, sinoatrial block, or third-degree atrioventricular block, (6) severe liver disease, (7) administration of ritonavir, josamycin, itraconazole, clarithromycin, cobicistat, indinavir, voriconazole,

nelfinavir, saquinavir, telaprevir, verapamil, or diltiazem, (8) confirmed or suspected pregnancy, lactation or planned pregnancy, (9) hypersensitivity to ivabradine, and (10) judged to be unsuitable by the principal investigator or sub-investigators at the hospital (site) for any other reasons.

Patients who meet all inclusion criteria and to whom none of the exclusion criteria apply will be enrolled in this study. After completed informed consent forms are obtained, patients will be given 5 mg/day of ivabradine during the study. Other drugs will not be changed after the start of administration of ivabradine. The physical examinations will be performed at baseline, 1 month, 2 months and 3 months after administration of ivabradine, and the 12-lead electrography, blood tests and echocardiography will be performed at baseline and 3 months after administration of ivabradine.

Echocardiographic examination

All patients will undergo a resting standard echocardiographic examination using commercially available echocardiography systems. Digital routine grayscale two-dimensional cine loops from three consecutive heart beats will be obtained at end-expiratory apnea from standard parasternal and apical views. Sector width will be optimized to allow for complete myocardial visualization while maximizing the frame rate. Standard echocardiographic measurements will be obtained in accordance with the current guidelines of the American Society of Echocardiography/European Association of Cardiovascular Imaging [18]. Specifically, the early diastolic (E) and atrial wave (A) velocities and the E-wave deceleration time will be measured by means of pulsed wave Doppler recording from the apical four-chamber view. Spectral pulsed-wave Doppler-derived early diastolic velocity (e′) will be obtained by averaging the septal and lateral mitral annulus, and the E/e′ ratio will be calculated to obtain an estimate of LV filling pressure. LA volume will be measured with the biplane Simpson's method from the apical two-and four-chamber views, and the LA volume index (LAVI) will be calculated by dividing LA volume by body surface area.

Speckle-tracking strain analysis for GLS

Speckle-tracking strain analysis will be performed for each patient with the aid of a single

dedicated software to evaluate LV longitudinal function, which will be assessed in terms of GLS (AutoStrain, Tom Tec-Arena; Tom Tec Imaging Systems GmbH, Unterschleissheim, Germany). Briefly, apical 4-, 2- and long-axis views together with the Digital Imaging and Communications in Medicine (DICOM) formatted file images will be uploaded onto a personal computer for subsequent off-line GLS analysis. Longitudinal speckle-tracking strain will be calculated by using an automated contouring detection algorithm, while manual adjustments of regions of interest will be made where necessary. Longitudinal strain results will be visualized color-coded in the individual clips and combined in a bull's eye plot. GLS will be then determined as the averaged peak longitudinal strain of 16 LV segments, and will be expressed as an absolute value in accordance with current guidelines [18].

Definition of primary endpoint

The primary end point will be defined as a change in E/e′ between baseline and 3 months after the start of administration of ivabradine, and the secondary end points as a change in brain natriuretic peptide (BNP), LAVI, or GLS between baseline and 3 months after the start of administration of ivabradine.

Sample size

Sample size and power calculations for the study are based on the assumption that the sample size calculation will be based on an expected E/e' of 13.5 at baseline and 11.0 at 3 months after administration of ivabradine with a standard deviation of 5.0. For reference, in another study the mean E/e' for HFpEF patients was determined as 12.8 [19]. Based on this assumption, a sample of 34 HFpEF patients will be required to detect a significant difference in E/e' between baseline and 3 months after administration of ivabradine with 80% power at a two-sided significance level of 5%, allowing for a drop-out of approximately 5 patients.

Statistical analysis

Continuous variables will be expressed as mean values with standard deviations for normally distributed data and as medians with interquartile ranges for non-normally distributed data. Categorical

variables will be expressed as frequencies and percentages. The parameters of the two groups between baseline and 3 months after the start of administration of ivabradine will be compared by using the paired-t test or the Wilcoxon signed-rank test depending on data distribution. Proportional differences will be evaluated with Fisher's exact test. For all steps, a p value of < 0.05 will be considered statistically significant. All the analyses will be performed with commercially available software.

Discussion

Impact of HR lowering on LV diastolic function in HFpEF patients

Sub-analysis of I-Preserve in 3271 HFpEF patients in sinus rhythm with an LVEF >45% and aged >60 years revealed that higher HR was associated with a significantly higher risk of all outcomes including primary endpoint of all-cause death or cardiovascular hospitalization, the composite of cardiovascular death or HF hospitalization, and all-cause death, even after adjustment for other prognostic variables [20]. High HR might be detrimental effect for HFpEF patients with LV diastolic dysfunction because of the limitation of LV filling. HR lowering will allow more time for LV filling and thus improve LV stroke volume and exercise tolerance. Thus, HR lowering therapy may have a positive impact on outcomes for HFpEF patients as it did for HFrEF patients, but the association of HR with LV diastolic function or impact of HR lowering on LV diastolic function remains unclear. Esfandiari et al. investigated the effects on LV diastolic function of increasing HR by controlling right atrial pacing in 11 HFpEF patients with LVEF<35% and 14 controls subjects [21]. The time constant of isovolumic relaxation was shortened in response to an increase in HR of both groups, but the slope of this relationship was steeper for HFrEF patients than for control subjects. The findings also showed the predicted volume at a theoretic pressure of 0 mmHg increased at higher HRs than at baseline, resulting in a shift to the right of the predicted the end-diastolic pressure-volume relationship compliance curve for HFrEF patients but not for control subjects.

There are no large randomized controlled trials to evaluate HR lowering with β-blockers or

ivabradine for LV diastolic function of HFpEF patients, who are currently defined for diagnosis as having an of LVEF ≥50% [16]. The prEserveD left ventricular ejectIon fraction chronic heart Failure with ivabradine studY (EDIFY) was a randomized, double-blind, placebo-controlled trial including 179 patients with NYHA functional class II and III, resting HR ≥70 bpm in sinus rhythm, and LVEF ≥45% [22]. Although HR of patients treated with ivabradine was significantly reduced with a median reduction of 13.0bpm over an 8-month follow-up, no significant change was observed in E/e'. A sub-analysis of the SHIFT study [23] showed that ivabradine reduced primary endpoint, all-cause mortality, cardiovascular mortality, HF death, and HF hospitalization of patients with HR ≥75 bpm, and that risk reduction depended on HR, with the optimal protection being HR <60bpm or reduction by >10bpm. In fact, none of these endpoints was significantly reduced for patients with HR 70-75 bpm, although risks of HF death and hospitalization ended to be reduced for HR<60 bpm and reduction by > 10bpm. Though still uncertain, the beneficial effect of ivabradine on LV diastolic function of HFpEF patients may be greater for patients with HR≥75 bpm. However, only HFpEF patients with HR ≥75bpm will enrolled in the IVA-PEF study. In addition, all patients enrolled in the EDIFY were symptomatic with higher BNP, E/e' and LAVI. This means that patients in the EDIFY had rather advanced HFpEF with extensive myocardial fibrosis compared to the IVA-PEF. This may be one of the reasons for poor response to ivabradine in HFpEF patients.

IVA-PEF will also include HFpEF patients with Stage A HF. The absolute mortality rate for HF remains approximately 50% within 5 years of diagnosis, although survival has improved[24]. A population cohort study reported that 5-year survival rates for Stages A, B, C, and D HF were 97%, 96%, 75%, and 20%, respectively[25]. Since Stage A HF is potentially useful for the implementation of HF prevention strategies, ivabradine may be useful for preventing eventual progression to overt HF such as Stages C and D even in Stage A HF patients with HR≥75 bpm.

Study limitations

Patients will be given 5 mg/day of ivabradine during the study, However, 70.9% patients in

the ivabradine group at the end of treatment form J-SHIFT study were on the highest dose of 15 mg/day. Thus, patients in this study may not reach optimal target HR.

Conclusion

We presented the rationale and design of the IVA-PEF to evaluate the effect of ivabradine on LV diastolic function of HFpEF patients. The findings of our trial may provide a new perspective on Ivabradine for the treatment of HFpEF.

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Disclosures: The authors declare no conflicts of interest.

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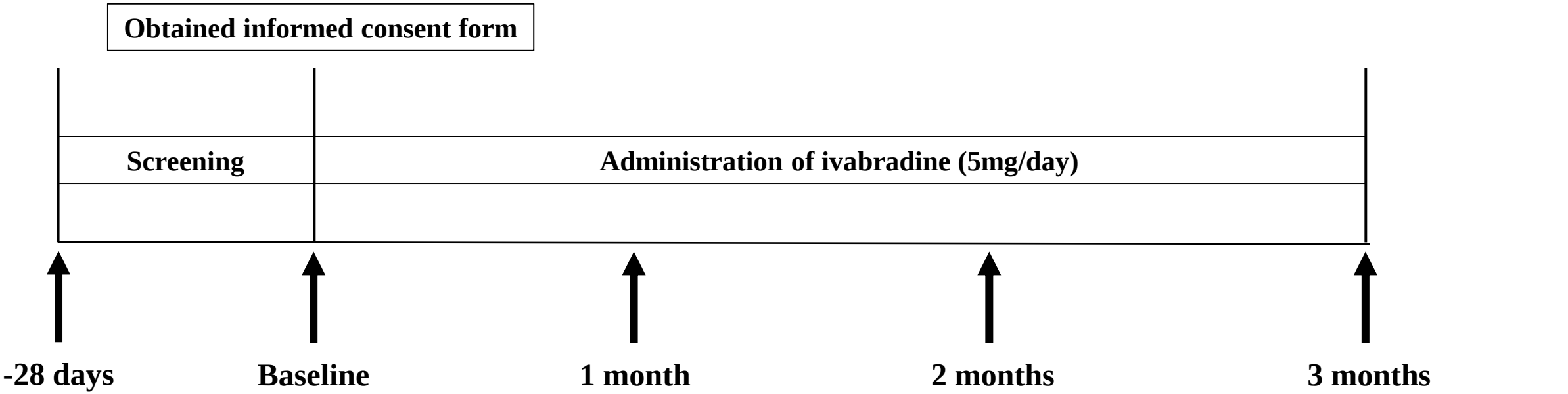
Figure Legends

Figure 1: Study Flowchart



- Physical examinations
- 12-lead electrocardiogram
- Blood tests
- Echocardiography

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