Effects of Heart Rate Reduction by Ivabradine for Heart Failure Beyond β-Blockers

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Ivabradine inhibits the If current in the sino-atrial node and reduces heart rate (HR) without affecting the autonomic nervous system or any action on other ionic cardiac currents, which is definitively different from the effects of β-blockers.1,2 Given these characteristics, previous clinical trials tried to confirm the additional effect of ivabradine on β-blockers in patients with heart failure (HF) and reduced ejection fraction (HFrEF).3,4 The first randomized controlled study was the BEAUTIFUL (morBidity-mortality EvAlUaTion of the If inhibitor ivabradine in patients with coronary disease and left-ventricular dysfunction) trial, which consisted of patients with stable coronary artery disease, EF <40%, sinus rhythm, and a resting HR of ≥60 beats/min.3 In the total cohort, no significant difference was found between ivabradine and placebo in terms of the primary composite endpoint (cardiovascular death, hospitalization for myocardial infarction and worsening HF).3 Second, the SHIFT (Systolic Heart failure treatment with the If inhibitor ivabradine inhibits the If current in the sino-atrial node and reduces heart rate (HR) without affecting the autonomic nervous system or any action on other ionic cardiac currents, which is definitively different from the effects of β-blockers.1,2 Given these characteristics, previous clinical trials tried to confirm the additional effect of ivabradine on β-blockers in patients with heart failure (HF) and reduced ejection fraction (HFrEF).3,4 The first randomized controlled study was the BEAUTIFUL (morBidity-mortality EvAlUaTion of the If inhibitor ivabradine in patients with coronary disease and left-ventricular dysfunction) trial, which consisted of patients with stable coronary artery disease, EF <40%, sinus rhythm, and a resting HR of ≥60 beats/min.3 In the total cohort, no significant difference was found between ivabradine and placebo in terms of the primary composite endpoint (cardiovascular death, hospitalization for myocardial infarction and worsening HF).3 Second, the SHIFT (Systolic Heart failure treatment with the If inhibitor ivabradine inhibits the If current in the sino-atrial node and reduces heart rate (HR) without affecting the autonomic nervous system or any action on other ionic cardiac currents, which is definitively different from the effects of β-blockers.1,2 Given these characteristics, previous clinical trials tried to confirm the additional effect of ivabradine on β-blockers in patients with heart failure (HF) and reduced ejection fraction (HFrEF).3,4 The first randomized controlled study was the BEAUTIFUL (morBidity-mortality EvAlUaTion of the If inhibitor ivabradine in patients with coronary disease and left-ventricular dysfunction) trial, which consisted of patients with stable coronary artery disease, EF <40%, sinus rhythm, and a resting HR of ≥60 beats/min.3 In the total cohort, no significant difference was found between ivabradine and placebo in terms of the primary composite endpoint (cardiovascular death, hospitalization for myocardial infarction and worsening HF).3 Second, the SHIFT (Systolic Heart failure treatment with the If inhibitor
The use of ivabradine was associated with an 18% reduction in heart rate (HR) in the primary composite endpoint of cardiovascular death or hospitalization for worsening HF, which mainly depended on admissions for worsening HF (hazard ratio 0.74, 95% confidence interval (CI) 0.66–0.83, P=0.0001). Thus, the BEAUTIFUL and SHIFT trials showed different results, although each population clearly differed in their primary diagnoses, particularly concerning the presence of HF. Indeed, all patients in the SHIFT trial had a history of HF and a recent hospitalization for the condition, whereas many of the patients in the BEAUTIFUL trial had no symptoms of HF. In addition, HR at baseline in the BEAUTIFUL trial was lower (71.6±9.9 beats/min) than in the SHIFT trial (79.2±9.6 beats/min). Therefore, the mean difference between the treatment groups (placebo minus ivabradine) in change from baseline resting HR at 1 year after randomization was smaller in the BEAUTIFUL trial (6.4 beats/min) than in the SHIFT trial (9.1 beats/min). Meanwhile, in the subgroup of the BEAUTIFUL trial with HR ≥70 beats/min (79.2±8.6 beats/min), hospitalization for acute myocardial infarction (hazard ratio 0.64, 95% CI 0.49–0.84, P=0.001) and coronary revascularization (hazard ratio 0.70, 95% CI 0.52–0.93, P=0.016) were diminished accompanied by a reduction in HR of 10 beats/min. These results suggested that the additional HR reduction induced by ivabradine is beneficial in patients with HR >70 beats/min despite β-blocker use. In particular, the magnitude of the HR reduction by ivabradine beyond what is achieved by β-blockers primarily determines the outcome.5

The beneficial effects of ivabradine are supported by alterations in hemodynamics and neurohumoral regulation (Figure). Both ivabradine and β-blockers reduce HR; however, ivabradine causes greater prolongation of diastolic time than β-blockers under a similar reduction in HR, because ivabradine does not have the negative lusitropic effect that β-blockers have.6,7 Also, ivabradine does not have an α-adrenergic coronary vasoconstriction effect, unlike β-blockers.8 These beneficial effects of ivabradine on coronary perfusion increase myocardial oxygen supply, showing anti-ischemic effects and improving exercise capacity.9 In addition, ivabradine administration increases stroke volume (SV) as an acute and chronic effect, which may be through Frank-Starling mechanics of increased left ventricular (LV) diastolic filling.9–12 As another hemodynamic mechanism, afterload reduction based on the mutual interaction of HR and effective arterial elastance (Ea) has been reported.9–12 Despite increased SV by ivabradine, blood pressure is not changed significantly, which maintains or decreases vascular resistance.9–12 The substudy of the SHIFT trial clearly demonstrated afterload reduction with improved arterial compliance.12 Namely, ventricular–arterial coupling was improved because of the reduction of Ea, resulting in higher SV in the ivabradine-treated patients.12 Meanwhile, experimental studies revealed a reduction in cardiac collagen and fibrosis with ivabradine.9,11,14 This pathological effect is related to diminished sympathetic activity caused by the improvement in LV filling. HR variability and significantly lower renin–angiotensin–aldosterone system activation induced by the decrease in HR.9,11,14 These pleiotropic effects in protecting LV structure and function by ivabradine create virtuous cycles, as shown in the Figure, which induces cardiac reverse remodeling.9,11,12,15 Because cardiac remodeling is a feature of HF progression, the beneficial effects of ivabradine on LV remodeling and function appear to have a central role in improving the prognosis of HFrEF patients receiving β-blockers.3,14

The Japanese SHIFT phase III study (J-SHIFT) was conducted to investigate the efficacy and safety of ivabradine in Japanese patients with HFrEF.18 This trial aimed to confirm the consistency of the results of the SHIFT trial rather than reveal the significant superiority of ivabradine compared with placebo, because of the small number of participants. As a result, J-SHIFT showed a decreasing trend for the primary composite endpoint of cardiovascular death or hospitalization for worsening HF (hazard ratio=0.67). In addition, as with the SHIFT trial, a significant reduction in hospitalization for worsening HF (hazard ratio=0.53, 95% CI 0.31–0.92, P=0.02), beneficial effects on cardiac remodeling and function, and no adverse side effects were revealed. The results from J-SHIFT may provide reliable information on the efficacy and safety of ivabradine use in Japanese HFrEF patients.

References

