CLINICAL INVESTIGATION

Ivabradine for the treatment of heart failure

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Several studies have underlined the beneficial effect of a lower heart rate on mortality in patients with chronic heart failure and reduced ejection fraction. In this context, the following review article will evaluate the benefit of a combination of the currently recommended pharmacological therapy in chronic heart failure (including β-blockers at optimal doses) with the selective heart rate reducing agent ivabradine. A summary of the basic pharmacology of ivabradine will precede the discussion of its efficacy and safety in clinical trials, as well as clinical implications.

Keywords: β-blockers • exercice tolerance • heart failure • heart rate reduction • ivabradine • left ventricular function • quality of life

In the recent European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure (HF), the heart rate (HR)-reducing agent ivabradine was added to the management of patients with heart failure and reduced ejection fraction (HF-REF), with the objective to reduce HF hospitalizations. Ivabradine is recommended if the left ventricular (LV) ejection fraction (EF) is ≤35%, heart rate is ≥70 bpm in sinus rhythm and there are persisting symptoms (NYHA class II–IV) despite treatment with an evidence-based dose of a β-blocker (or maximum tolerated dose), an angiotensin converting enzyme inhibitor (or angiotensin-receptor blocker) and a mineralocorticoid receptor antagonist (class IIa); or if β-blockers are not tolerated (class IIb) [1]. Ivabradine is a HR-reducing agent acting through selective inhibition of the funny current (*If*) in the sinus node. The *If* current, an inward current activated by hyperpolarization, is a major player in both the generation of spontaneous cardiac electrical activity and HR control [2]. This selective HR reduction decreases myocardial oxygen demand and increases diastolic duration, allowing increased coronary flow and thus improving oxygen supply, without directly affecting inotropy [3–5]. Ivabradine's mechanism of action selectively targets the *If* current; hence it only affects this pacemaker current [6] and does not directly alter other cardiovascular parameters (blood pressure, ventricular repolarization, myocardial contractility and relaxation) [6,7].

Basic pharmacology & pharmacokinetics

Pharmacokinetics

Ivabradine is rapidly released from the tablets administered orally, and then is rapidly and almost completely absorbed systemically with the peak plasma level reached in almost 1 h under fasting conditions [8]. The absolute bioavailability of the film-coated tablets is approximately 40% due to the first-pass metabolism of ivabradine by the gut and liver, which is responsible for 80% of its elimination [8]. The remaining 20% of elimination is through renal excretion and 4% of the parent drug is excreted unchanged. The isoenzyme primarily responsible for the metabolism of ivabradine is CYP450 3A4 (CYP3A4) [8] and its major active metabolite is the N-demethylated derivative S-18982 (the latter contributes to the effect of ivabradine on HR and has the same model

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Table 1. The pharmacokinetics of ivabradine and its major metabolite S-18982.

Drug	T_{max} (h)	$T_{1/2}$ (h)	Absolute bioavailability (p.o. film-coated tablets)	Metabolism	Elimination	Drug–drug interaction: contraindication	Dose adjustment according to disease	Other contraindications
Ivabradine p.o.	≈ 1.0	≈ 2.0	40%	Liver and intestinal oxidation with CYP3A4	80% metabolic 20% renal (4% unchanged)	Potent inhibitors of CYP3A4: azole antifungals, macrolides; HIV protease inhibitors; nefazodone	Caution when CrCL <15 ml/min; contraindication with severe hepatic insufficiency	Hypersensitivity to ivabradine or to any of the excipients HR <60 bpm prior to treatment; cardiogenic shock; acute myocardial infarction; BP <90/50 mmHg; sick sinus syndrome; unstable angina; third-degree AV-block pregnancy and lactation
S-18982	≈ 1.0	≈ 4.40	NA	CYP3A4	80% metabolic 20% renal			

CrCl: Creatinine clearance; NA: Not applicable; p.o.: Oral administration; T_{max}: Time to reach maximal plasma concentration after administration; $T_{1/2}$: Elimination half-life.

of elimination: 80% metabolic and 20% renal) [8]. Ivabradine is a very weak inhibitor of CYP3A4, hence it is unlikely to influence the metabolism and plasma concentrations of other CYP3A4 substrates. However, inducers of CYP3A4 (rifampicin, barbiturates, phenytoin and St John's Wort) may decrease ivabradine concentrations and may require a dose increase. Also, strong inhibitors of CYP3A4 will increase ivabradine concentrations and their concomitant use with this agent is contraindicated [8]. Table 1 summarizes the pharmacokinetic characteristics of ivabradine and S-18982 [8].

Pharmacodynamics

HR reducing effect & mechanism of action

Ivabradine exerts its HR reducing effect through the inhibition of the *If* in the sinus node. The *If* is an inward Na^+/K^+ current activated by hyperpolarization. With oral administration of ivabradine in a dose range of 0.5–24 mg, HR has been shown to decrease in an almost linear manner when doses are increased, but this relationship becomes nonlinear at higher dosages and the decrease in HR achieved eventually reaches a plateau.

The pacemaker *If* current is mediated by the hyperpolarization-activated cyclic nucleotide gated channels (HCN), which have four isoforms in mammals [9,10]. In humans the HCN 4 isoform is predominantly present in sino-atrial node cells [11]. Ivabradine's binding site is located on the inner side of HCN4 channels, which results in their blockade only when they are in an activated open state [12]. Intracellular blockade of the *If* current by ivabradine is use dependent [6,13–16], meaning that the pharmacological effect will be more marked when HCN channels are more often open and HR is more rapid. At the other end of the spectrum, ivabradine's HR reducing effect will be much more limited when HR is already low (because HCN channels are less frequently open).

In vivo animal experiments have revealed the acute HR-reducing effect of ivabradine when administered intravenously [17]. An open-label study in humans [18] found similar results, with no change in the electrophysiological parameters of the cardiac conduction system, which was confirmed by the lack of change in the PR, QRS and corrected QT intervals on the electrocardiogram. The potential for QT interval prolongation was proposed after animal studies [6] but arrhythmogenic ventricular effects are absent at recommended doses in humans. Nonetheless, concomitant use of QT prolonging agents with ivabradine should be avoided since QT prolongation may be increased with HR reduction. However, if such a combination is necessary, close cardiac monitoring is required [8].

Hemodynamic effects & mechanisms of action

Animal studies

The acute hemodynamic changes after administration of ivabradine were compared with those observed with β-blockers (atenolol and propanolol) at rest and during exercise in healthy dogs [7,19]. During exercise, ivabradine and propranolol significantly decreased HR to similar extents. However, the reduction in coronary artery diameters and in myocardial inotropy was less pronounced with ivabradine than with propanolol [7,17]. Prolongation of the cycle length prolongs diastole, leading to an increase in myocardial oxygen supply and a decrease in demand, resulting in an improved oxygen supply:demand ratio [20]. Heart rate reduction with ivabradine correlates significantly with improvements in left ventricular end-diastolic volume, left ventricular end-systolic volume and left ventricular ejection fraction (LVEF) [20]. Finally, ivabradine improves both regional coronary blood flow as well as the contractile function of the heart [21].

Human mechanistic studies

Two small studies have described the beneficial effects of ivabradine on LV hemodynamics in patients with HF-REF [22,23]. The first study [22] was a randomized, single-blind, placebo-controlled study. A total of 44 patients with systolic LV dysfunction (LVEF between 20 and 50% within 3 months prior to the study) in sinus rhythm with HR ≥ 60 bpm were randomized to receive either intravenous ivabradine (n = 31) 0.25 mg/kg or placebo (n = 13). The primary evaluation criterion was LVEF and the secondary criteria were fractional shortening and stroke volume. The second study [23] was an open-label pilot study of ten patients with severe congestive HF (NYHA class III) and LV systolic dysfunction (LVEF <35%). Patients had to be in sinus rhythm with resting HR ≥80 bpm. Ivabradine was infused at a dose of 0.1 mg/kg first, followed by a dose of 0.075 or 0.05 mg/kg, depending on the HR. The infusion was stopped if HR fell below 60 bpm. Hemodynamic measurements (including cardiac output, cardiac index and stroke volume) were obtained using a Swan-Ganz catheter at different intervals before, during and after the infusion. LV end-systolic and end-diastolic volumes, as well as EF, were obtained through echocardiographic evaluation. Ivabradine significantly decreased HR in both studies (from baseline and compared with placebo).

In the first study, an increase in LVEF was observed with ivabradine compared with placebo (2.9% increase in EF from baseline with ivabradine vs 0.3% increase from baseline with placebo, p-value not reported), as was the case for stroke volume (3.6-ml increase from baseline with ivabradine vs 7.4-ml decrease with placebo, p-value not reported) [22]. In the second study, despite a significant reduction in HR (93 bpm at baseline vs 82 bpm after 24 h; $p < 0.01$), cardiac index was maintained and tended to increase (2.2 l/min/m^2 at baseline vs 2.5 l/min/m^2 at 24 h; $p = 0.15$) [23]. Hence, ivabradine did not demonstrate intrinsic negative inotropic properties (it increased stroke volume and preserved cardiac output), which confirms the previously described pharmacologic properties.

Ivabradine as a therapeutic agent & the importance of HR reduction in heart failure

Elevated resting HR is an independent predictor of mortality and morbidity in multiple cardiovascular diseases, including chronic HF (with reduced or preserved EF). An elevated HR creates an imbalance between oxygen supply and demand in the myocardium and is associated in experimental models with vascular oxidative stress, endothelial dysfunction, acceleration of atherogenesis and coronary plaque instability [24]. A high HR also likely contributes to the development of atherosclerosis through an increase in arterial stiffness [25]. In chronic HF, an increased HR worsens already impaired cardiac efficiency [25].

β-blockers remain first-line agents recommended for the treatment of patients with chronic HF-REF [1]. These agents are known to improve prognosis proportionally to HR reduction [26,27] and to significantly decrease mortality compared with placebo [28–32] through different mechanisms. β-blockers inhibit progression of HF and prevent sudden arrhythmic deaths [33,34]. Overall, a reduction in HR to reach values lower than 70 bpm improves survival in patients with HF-REF treated with β-blockers [26,27,35–37].

Clinical effects of ivabradine in heart failure & systolic dysfunction

The BEAUTIFUL trial [38] was a multinational randomized clinical trial assessing the effect of ivabradine on mortality and morbidity in 10,917 patients with stable coronary artery disease, LVEF <40%, sinus rhythm and HR ≥60 bpm. The starting dose of ivabradine (and matched placebo) was 5 mg twice daily (b.i.d.) and the dose was then evaluated at 2 weeks: in patients with HR ≥60 bpm the dose was increased to 7.5 mg b.i.d., and the dose was reduced back to 5 mg b.i.d. if HR <50 bpm, or if they had signs or symptoms related to bradycardia. The study drug was discontinued in patients treated with 5 mg b.i.d. if HR was less than 50 bpm or if they had signs or symptoms related to bradycardia. Although ivabradine did not reduce the primary composite end point of cardiovascular death or admission to hospital for myocardial infarction or

new-onset or worsening HF, it did reduce the incidence of the secondary end point of fatal and nonfatal myocardial infarction in patients with a baseline HR ≥70 bpm.

The SHIFT trial [39] included only patients with HF (classes II to IV), LVEF ≤35%, sinus rhythm and a HR ≥70 bpm. This trial involved 6505 patients from 677 centers in 37 countries, followed for a median duration of 22.9 months. Patients needed to be on optimal and stable background treatment for at least 4 weeks (≈90% of patients were on β-blocker therapy, of which 56% received at least 50% of the target dose). The starting dose of ivabradine was 5 mg b.i.d. After a 14-day titration period, the ivabradine dose was increased to 7.5 mg b.i.d. unless the resting HR was ≤60 bpm. If HR was between 50 and 60 bpm, the dose was maintained at 5 mg b.i.d. If the resting HR was lower than 50 bpm or the patient had signs or symptoms related to bradycardia, the dose was reduced to 2.5 mg b.i.d. Ivabradine decreased the relative risk of cardiovascular death or hospital admission for worsening HF (primary end point) by 18% compared with placebo ($p < 0.0001$), while hospitalizations for HF and deaths due to HF were both reduced by 26%. The effect was consistent across all prespecified subgroups, although it did not reach statistical significance in the subgroup with a baseline HR lower than the median of 77 bpm. In addition, ivabradine was well tolerated in patients with HF-REF on top of recommended optimal pharmacological therapy. A significant reduction in recurrent hospitalizations for worsening HF associated with ivabradine therapy ($p < 0.001$ vs placebo) has also been documented in an ancillary SHIFT study [40]. Recurrent hospitalizations constitute an increasingly important objective in the assessment of HF treatments, as these are expected to have a major impact on quality of life and healthcare economics.

Table 2 summarizes the inclusion and exclusion criteria, as well as the main results of the BEAUTIFUL and SHIFT trials. It is important to specify that patients with chronic atrial fibrillation or flutter were excluded from these studies since the target of ivabradine is the sinus node. The prevalence of atrial fibrillation in HF overall ranges between 13 and 27% in modern series [41]. Moreover, the use of cardiac devices in the SHIFT trial was low (cardiac resynchronization therapy and implantable cardioverter defibrillator in 1 and 4% of patients, respectively), in agreement with the study design (exclusion if ventricular or atrioventricular pacing was operative for 40% or more of the day).

A pooled analysis of the results of both SHIFT and BEAUTIFUL trial (n = 11,897) included all the patients from both trials with a baseline HR ≥70 bpm [42]. The mean HR at baseline was 79.6 ± 9.2 bpm and the mean EF was 30.3 ± 5.6%, with no significant differences between treatment groups. Both SHIFT and BEAUTIFUL end points (Table 2) were analyzed. There was a 13% relative risk reduction in cardiovascular mortality or hospitalization for HF ($p < 0.001$), mainly driven by the impact on HF hospitalization ($p < 0.001$). Significant risk reductions were also observed for the composite outcomes of cardiovascular mortality, HF hospitalizations, or myocardial infarction (MI) hospitalization (15%; $p< 0.001$); cardiovascular mortality and nonfatal MI (10%; $p = 0.023$); and MI hospitalization (23%; $p = 0.009$). The differences between the studies (β-blockers dosage, clinical severity of cardiac dysfunction) were taken into account in this analysis. The authors concluded that ivabradine improved outcomes in a broad population of patients with LV systolic dysfunction, whether HF etiology was ischemic or nonischemic (see exclusions in Table 2), and across the spectrum of LVEFs and NYHA classes recorded in these trials.

Regarding the impact of ivabradine in patients with severe HF (n = 712), a recent *post hoc* study of SHIFT [43] showed that these patients had poorer outcomes compared with patients with less severe HF (n = 5973), and that higher HR accentuated this effect. In the 272 patients with severe HF and a HR ≥75 bpm (HR threshold for approved indication by the EMA), ivabradine reduced the SHIFT primary outcome by 25% ($p = 0.045$), as well as HF hospitalizations by 30% ($p = 0.042$) and cardiovascular death by 32% ($p = 0.034$). The safety profile of ivabradine did not differ between the severe HF and the less severe HF groups.

Finally, it appears that patients with chronic obstructive pulmonary disease (COPD) receive lower doses of β-blockers and less often receive the target doses of these agents, as demonstrated in a recent SHIFT publication [44] comparing the benefits of ivabradine between the subgroups of patients with a history of COPD and those without this comorbid condition. Although patients with COPD (n = 730) had a higher resting HR, a lower EF ($p < 0.001$) and higher NYHA class compared with non-COPD patients, only 69% of COPD patients were treated with β-blockers at randomization compared with 92% of non-COPD patients ($p < 0.001$). The SHIFT primary end point and HF hospitalizations were similarly reduced with ivabradine in both COPD (14 and 17%, for the primary and HF hospitalization end points, respectively) and non-COPD (18 and 27%) patients (p for interaction = 0.82 and 0.53, respectively). Although the diagnosis and severity of COPD were not formally evaluated in SHIFT and the above findings should be interpreted with caution given the *post hoc* nature of

Table 2. Summary of the main clinical trials of ivabradine in systolic left ventricular dysfunction and heart failure.

Inclusion	Exclusion	Results
BEAUTIFUL [38]		
Age ≥55 years CAD, LVEF <40%, LV end-diastolic short-axis internal dimension greater than 56 mm by echocardiography Sinus rhythm with HR >60 bpm Angina and HF symptoms stable for at least 3 months (if present) Appropriate conventional cardiovascular medication at stable doses for at least 1 month	MI or coronary revascularization in the previous 6 months Stroke or TIA in the previous 3 months Implanted pacemaker, cardioverter or defibrillator Valvular disease needing surgery within the next 3 years Sick sinus syndrome; sinoatrial block; congenital long QT; complete atrio-ventricular block; severe or uncontrolled hypertension NYHA class IV Treatment with strong CYP450 3A4 inhibitors	**In the total population, there were no significant reductions of:** Cardiovascular death or admission to hospital for MI or new-onset or worsening HF in overall population (primary end point) All-cause mortality (all cause, cardiovascular and cardiac causes) Heart failure end points (admission to hospital for HF; cardiovascular death or admission to hospital for new-onset or worsening HF) Coronary end points (admission to hospital for MI; admission to hospital for MI or unstable angina) **In patients with HR ≥70 bpm:** Reduction in rates of hospital admissions for acute MI (hazard ratio: 0.64; 95% CI: 0.49–0.84; p = 0.001) Reduction in rates of hospital admissions for acute MI or unstable angina (hazard ratio: 0.78; 95% CI: 0.62–0.97; p = 0.023) Reduction in coronary revascularizations (hazard ratio: 0.70; 95% CI: 0.52–0.93; p = 0.016)
SHIFT [39]		
Age ≥18 years Stable symptomatic chronic HF of ≥4 weeks duration Admission to hospital for worsening HF within the previous 12 months LVEF ≤35% Any cause of HF apart from congenital heart disease or primary severe valvular disease Sinus rhythm with HR ≥70 bpm Optimum and stable background treatment for at least 4 weeks	Recent (<2 months) MI Ventricular or atrioventricular pacing operative for 40% or more of the day Atrial fibrillation or flutter Symptomatic hypotension Nondihydropyridine calcium-channel blockers, class I antiarrhythmics, and strong inhibitors of CYP450 3A4	Reduction (by 18%) in primary end point of cardiovascular deaths or hospital admissions for worsening HF (hazard ratio: 0.82; 95% CI: 0.75–0.90; p < 0.0001) Effect driven mainly by hospital admissions for worsening HF (hazard ratio: 0.74; 95% CI: 0.66–0.83; p < 0.0001) Cardiovascular deaths not significantly reduced with ivabradine (hazard ratio: 0.91; 95% CI: 0.80–1.03; p = 0.128) Deaths due to HF decreased significantly with ivabradine (hazard ratio:0.74; 95% CI: 0.58–0.94; p = 0.014)

CAD: Coronary artery disease; HF: Heart failure; HR: Heart rate; LV: Left ventricle; LVEF: Left ventricular ejection fraction; MI: Myocardial infarction; NYHA: New York Heart Association class; TIA: transient ischemic attack.

the ancillary study, patients with HF and COPD constitute a high risk group where β-blockers are underused and where the outcome benefits of ivabradine are significant.

Relationship between event reduction & HR reduction with ivabradine

In an ancillary analysis of the placebo arm of the BEAUTIFUL trial [45], patients (n = 5438) were separated in two groups depending on HR at baseline (<70 bpm vs ≥70 bpm). In the group of patients with HR 70 bpm, there was a 34% increase in the adjusted relative risk of cardiovascular death (p = 0.0041) and a 53% increase in adjusted relative risk of admission to hospital due to HF (p < 0·0001) compared with those with lower HR. For every increase in HR by 5 bpm, there was an 8% increase in cardiovascular death (p = 0.0005), and a 16% increase in admissions to hospital for HF (p < 0.0001). In an ancillary analysis of SHIFT [46], patients with the more pronounced HR reductions with ivabradine had the greatest reduction in rates of the primary composite outcome (p < 0.0001). Also, patients with the highest baseline HR achieved the highest reductions in HR. In addition, there was a neutralization of the beneficial effects of ivabradine after adjustment for change in HR. Hence, in patients with chronic HF-REF the beneficial effects of ivabradine appear to be mainly related to its pure HR-reducing effect. Nonetheless, other potential mechanisms explaining the improvement of outcomes of HF patients with ivabradine have been suggested but further studies are still needed to confirm these HR independent effects [47,48].

Relationship between ivabradine effects & β-blocker doses

In another SHIFT ancillary analysis [49], the primary and secondary end points were not significantly (p = 0.135) related to the doses of β-blockers received, even after adjustment for baseline HR. However, there was a numerical reduction of the beneficial effect of ivabradine with higher doses of β-blockers (Table 3). Overall, β-blocker doses do not appear to significantly modulate the beneficial effects of adding ivabradine on top of other recommended therapy in HF patients with a HR of 70 bpm or more.

Effects of ivabradine on LV structure & function and on arterial elastance

LVEF and LV volumes are powerful predictors of cardiovascular events in HF patients [50]. In an ancillary study of the BEAUTIFUL trial [51], LVEF increased significantly in the ivabradine group compared with the placebo group (p = 0.009). In the ivabradine group there was a slight reduction in the LV end-systolic volume index (LVESVI). In contrast with the placebo group this value mildly increased (p = 0.018). The LV end-diastolic volume index (LVEDVI) did not significantly change in the ivabradine group and increased in the placebo group (p = 0.165). In the SHIFT echocardiography substudy [52], the incidence of the primary clinical composite end point in the placebo group was significantly greater in patients with larger LVESVI and LVEDVI, confirming the prognostic value of LV volumes. Ivabradine at a mean dose of 6.0 mg b.i.d. decreased both LVESVI and LVEDVI compared with placebo (p < 0.001), confirming its favorable effect on LV reverse remodeling. Also, there was a significant improvement of LVEF in the ivabradine group compared with placebo (p < 0.001).

A recently published ancillary study of the SHIFT trial demonstrated that unloading of the heart by ivabradine may contribute to its beneficial effect in patients with systolic HF [53]. In that study, HR reduction with ivabradine improved the efficiency of LV contractile function as a consequence of an improvement in ventricular–arterial coupling. Effective arterial elastance (Ea), which combines both mean and pulsatile vascular load, reflecting the impact of vascular load on LV function, significantly decreased after 8 months of treatment with ivabradine compared with placebo (p < 0.0001). Total arterial compliance significantly increased from baseline with ivabradine compared with placebo (p < 0.001), while LV end-systolic elastance, representing ventricular contractility, was not significantly different in the ivabradine group compared with placebo. There was a significant (p < 0.001) increase in Ea and a significant (p < 0.001) decrease in total arterial compliance at higher baseline HR, which implies an increased vascular load on the LV at higher HR. Furthermore, the ratio of Ea/end-systolic elastance representing vascular-ventricular coupling (similar at baseline in the two groups) significantly decreased in the ivabradine group compared with baseline and to placebo. Therefore, treatment with ivabradine improves the efficiency of LV work, as shown in Figure 1, which explains the increase in stroke volume with ivabradine, even if this agent does not affect inotropy. Indeed, despite a similar slope of end-systolic pressure–volume relationship, representing contractility, the stroke volume increased after treatment with ivabradine.

Effects of ivabradine on quality of life & exercise tolerance in patients with heart failure

Ivabradine improves exercise capacity and quality of life (QoL) compared with placebo in patients with

Table 3. Effects of β-blocker doses on the primary end points of the SHIFT trial.

Primary end point	Hazard ratio vs placebo (p-value)	Heterogeneity
No β-blocker	0.71 (0.55–0.93; p = 0.012)	p = 0.35
β-blocker dose <25%†	0.74 (0.59–0.92; p = 0.007)	Trend
β-blocker dose 25–50%†	0.81 (0.68–0.98; p = 0.029)	p = 0.056
β-blocker dose 50–100%†	0.88 (0.72–1.07; p = 0.193)	Trend, interaction adjusted
β-blocker dose ≥100%†	0.99 (0.79–1.24; p = 0.913)	p = 0.135
Hospital admission for worsening HF		
No β-blocker	0.62 (0.45–0.85; p=0.003)	p = 0.55
β-blocker dose <25%†	0.68 (0.52–0.89; p=0.005)	Trend
β-blocker dose 25–50%†	0.74 (0.59–0.93; p=0.009)	p = 0.12
β-blocker dose 50–100%†	0.83 (0.65–1.05; p=0.119)	Trend, interaction adjusted
β-blocker dose ≥100%†	0.84 (0.63–1.11; p=0.223)	p = 0.19
CV death		
No β-blocker	0.80 (0.57–1.12; p = 0.192)	p = 0.68
β-blocker dose <25%†	0.82 (0.61–1.09; p = 0.172)	Trend
β-blocker dose 25–50%†	0.95 (0.74–1.22; p = 0.696)	p = 0.17
β-blocker dose 50–100%†	0.99 (0.75–1.31; p = 0.930)	Trend, interaction adjusted
β-blocker dose ≥100%†	1.08 (0.78–1.48; p = 0.646)	p = 0.30

†Percent of target doses.
CV: Cardiovascular; HF: Heart failure.
Adapted with permission from [49].

HF [54]. In the latter study, ivabradine significantly increased exercise endurance, peak oxygen uptake and oxygen consumption at the anaerobic threshold compared with baseline, after 3 months of treatment ($p < 0.0001$). No significant differences were noted in the control group at 3 months. Moreover, there was a significant improvement in QoL (as evaluated with the Minnesota questionnaire scores) at 3 months in the ivabradine group compared with baseline ($p < 0.0001$). Significant improvement in QoL with ivabradine was also demonstrated in SHIFT [55]. In total, 24 centers participated in the QoL study, and a total of 2282 patients underwent an assessment of QoL with the disease-specific Kansas City Cardiomyopathy Questionnaire, at baseline, at 4, 12 and 24 months of randomized treatment, and at last visit. Treatment with ivabradine significantly improved Kansas City Cardiomyopathy Questionnaire scores compared with placebo (1.8 for the clinical summary score, $p = 0.018$ and 2.4 for the overall summary score, $p = 0.001$), and this was maintained until the last visit. There was an association between improvement in QoL and HR reduction for both scores in the ivabradine and in the placebo group.

The CARVIVA study [56] explored the benefits of ivabradine on exercise tolerance compared with standard therapy with a β-blocker in patients with HF. In total, 121 patients were included. In patients receiving β-blockers these drugs were gradually discontinued, and the angiotensin converting enzyme inhibitors were uptitrated to optimal doses recommended. After the assessment of the baseline exercise capacity parameters, patients were randomly allocated to three groups: carvedilol up to 25 mg b.i.d.; ivabradine up to 7.5 mg b.i.d.; and combination carvedilol/ivabradine up to 12.5/5 mg b.i.d. HR significantly decreased with the combination of ivabradine and carvedilol, compared with carvedilol alone ($p < 0.05$). In addition, there were significant improvements in maximal oxygen consumption and 6-min walking distance in the ivabradine and combination therapy groups compared with the carvedilol-only group ($p < 0.01$ and $p < 0.02$, respectively).

Ivabradine in HF with preserved ejection fraction?

In a recent small study of 61 patients [57], ivabradine (5 mg b.i.d. for 7 days) had a significant beneficial effect on maximal exercise capacity in patients with HF and preserved ejection fraction (HF-PEF). The study showed an improvement in diastolic function during exercise, including an improvement in LV filling pressures (revealed by the E/e' ratio). The latter was due to a combination of factors including an increase in filling

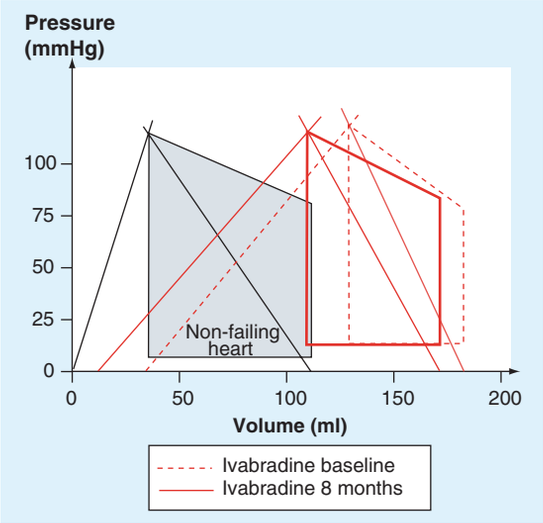

Figure 1. The effect of ivabradine on the pressure–volume loop of the left ventricle in heart failure.
Ivabradine treatment over 8 months reduced afterload, thereby improving ventricular–arterial interaction with a marked increase in stroke volume (red solid loop). Note the prominent leftward shift of the x-axis intercept of end-systolic pressure volume relationship of the ivabradine group (solid vs dotted lines), indicating LV reverse remodeling.
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time (secondary to a reduction in HR), acceleration of myocardial relaxation and improvements of arterial stiffness and endothelial function. Larger studies are needed to confirm the potential beneficial role of ivabradine in HF-PEF.

Safety of ivabradine

The most common adverse events noted with ivabradine are bradycardia and visual symptoms called phosphenes. The latter are defined as transient enhanced brightness in a limited area of the visual field, triggered by sudden variations in light intensity [58]. They are due to the interaction of ivabradine with the retinal current *Ih*, and they occur generally within the first 2 months of treatment and resolve during or after treatment [58]. This phenomenon does not interfere with quality of life or daily activities, [59] but may be taken into consideration when driving in situations where sudden changes in light intensity can occur, such as driving at night.

In the BEAUTIFUL trial [38], with the exclusion of the study end points and other coronary and HF events, 23% of patients in the ivabradine and the placebo groups experienced serious adverse events. In total, 28% and 16% of patients in the ivabradine and control groups respectively discontinued the study medication, and bradycardia was the reason for discontinuation in 6% of patients in the ivabradine group and 1% of controls. Also, 0.5% of patients in the ivabradine group and 0.2% in the placebo group withdrew from the study because of visual symptoms, which disappeared after treatment discontinuation. A substudy of the BEAUTIFUL trial evaluated cardiac safety of ivabradine in patients with coronary artery disease and LV dysfunction with concomitant use of optimal therapy (93% of patients were using β-blockers). The incidence of bradycardia <30 bpm was less than 1% in both the ivabradine and placebo groups. Ambulatory 24-h Holter monitoring was performed at baseline, after 1 and 6 months, and a safety analysis performed on 807 patients from the original study concluded that there was no increase in incidence of conduction and rhythm disturbances with ivabradine in comparison to placebo [60]. The increase in the corrected QT interval (QTc) related to the bradycardic action of ivabradine does not hold ventricular arrhythmogenic potential [59]. This was confirmed by the BEAUTIFUL Holter substudy, where there was no significant difference between the ivabradine and placebo groups in the incidence of ventricular tachycardia [60]. In the BEAUTIFUL and SHIFT studies, amiodarone was not an exclusion criterion and was used in 5.9 and 2.9% of patients, respectively [49,51].

In the SHIFT trial [39], ivabradine was overall well tolerated with at least 70% of patients at target dose (7.5 mg b.i.d.) after 1 year. The total number of cardiac and noncardiac serious adverse events was lower in the ivabradine group compared with the placebo group ($p = 0.025$). Bradycardia occurred in 10% of patients (90% of patients were on β-blockers with 49% at ≥50% of the target β-blocker dose) and symptomatic bradycardia occurred in 5% of the ivabradine group and 1% of the placebo group ($p < 0.0001$). Only 1% of patients stopped study medication owing to this side effect. The incidence of atrial fibrillation was similar between the treatment and placebo groups (9 and 8%, respectively). Visual symptoms were rare in the ivabradine group (3% of patients experienced phosphenes and 1% experienced blurred vision) and less than 2% of patients stopped study medication because of the latter.

No pharmacokinetic differences have been observed between patients older than 65 years and the overall population with this agent, but ivabradine has been studied in a limited number of patients older than 75 years. Hence, a lower starting-dose should be considered for this group of patients (2.5 mg b.i.d.), which then could be uptitrated based on clinical response. Ivabradine should be avoided or used with caution in patients with impaired hepatic function, since there is insufficient safety data in this group [8]. In patients with a creatinine clearance greater than 15 ml/min,

changes in the pharmacokinetic of ivabradine are minimal. However, for patients with a creatinine clearance less than 15 ml/min, no data are available, and ivabradine should be used with caution in this population. Also, as seen previously, ivabradine cannot be used concomitantly with strong inhibitors of the CYP3A4 (Table 1).

Conclusion

In summary, when the HR is 70 bpm or more despite optimal therapy in patients with HF [1], ivabradine should be considered to improve prognosis, exercise tolerance and QoL. Based on the SHIFT trial, a starting dose of 5 mg b.i.d. is recommended, which can be increased to 7.5 mg b.i.d., unless the resting HR is <60 bpm (then 5 mg b.i.d. should be continued). If resting HR is <50 bpm or the patient has signs or symptoms related to bradycardia, the 5 mg b.i.d. dose should be reduced to 2.5 mg b.i.d. Ivabradine cannot be used to control HR in patients with atrial fibrillation, and its benefits are not demonstrated in patients with HF-REF and a pacemaker (or cardiac resynchronization therapy) device providing ventricular or atrioventricular pacing operative for 40% or more of the day.

Financial & competing interests disclosure

J-C Tardif has received research grants and honoraria from Servier. E O'Meara has received research grants from Johnson & Johnson Canada, Servier Canada, and les Fonds de Recherche Santé-Québec. E O'Meara has served as a consultant and/or presenter for Pfizer, Novartis and Servier. S de Denus has received research grants from Hoffmann-La Roche Canada, Novartis Pharmaceuticals Canada, Pfizer Canada, AstraZeneca Canada and Johnson & Johnson, as well as consulting fees from Servier Canada. S de Denus was also a presenter for Pfizer Canada. S de Denus holds the Université de Montréal Beaulieu-Saucier Chair in Pharmacogenomics. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- A lower heart rate (HR) is associated with a better prognosis in heart failure (HF).
- Ivabradine, a selective HR-reducing agent, does not negatively affect inotropy or hemodynamics.
- Ivabradine safely reduces the composite of cardiovascular mortality and HF hospitalizations in patients with HF and reduced ejection fraction when HR remains ≥70 bpm despite optimal recommended therapy (including maximally tolerated doses of β-blockers).
- The addition of ivabradine to optimal pharmacological HF therapy improves left ventricular structure and function (inducing reverse left ventricular remodeling), exercise tolerance and quality of life in patients with HF and reduced ejection fraction.

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