



Review Article

Ivabradine: Evidence and current role in cardiovascular diseases and other emerging indications

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ABSTRACT

Increased heart rate (HR) is associated with deleterious effects on several disease conditions. Chronic heart failure (CHF) is one of the cardiovascular diseases with recurrent hospitalization burden and an ongoing drain on health-care expenditure. Despite advancement in medicine, management of CHF remains a challenge to health-care providers. Ivabradine selectively and specifically inhibits the pacemaker I(f) ionic current which reduces the cardiac pacemaker activity. The main effect of ivabradine therapy is the substantial lowering of HR. It does not influence intracardiac conduction, contractility, or ventricular repolarization. As shown in numerous clinical studies, ivabradine improves clinical outcomes and quality of life and reduces the risk of death from heart failure (HF) or other cardiovascular causes. Recently updated HF guidelines recommend ivabradine as a class II indication for reduction of HF hospitalizations. Based on the principle of benefits of reduced HR, the ivabradine in patients with ischemic heart disease, sepsis, and multiple organ dysfunction syndrome has also been studied. It can also be a useful agent for HR reduction in patients with contraindications to use beta-blockers or those who cannot tolerate them. In this review, we provide an overview of efficacy and safety of ivabradine and its combination with currently recommended pharmacological therapy in different conditions.

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1. Introduction

Cardiovascular diseases (CVD) are a leading cause of death and disability as well as major public health burden worldwide. CVD covers a wide range of illnesses related to the circulatory system including coronary artery disease (CAD), heart failure (HF), and stroke. HF is a clinical syndrome caused by structural and functional defects in myocardium resulting in impairment of ventricular filling or ejection of blood. HF is a growing health concern worldwide with over 37.7 million people being affected by it¹ (Figs. 1 and 2).

During the last decade, very few newer drugs including ivabradine have been introduced for the management of HF.

Ivabradine is indicated in symptomatic treatment of chronic stable angina, HF, and also in those who are unable to tolerate or have contraindications to the use of beta-blockers. Previous

guidelines mandated that patients should have a heart rate (HR) of 60 bpm or higher for using ivabradine. However, various regulatory agencies now recommend the use of ivabradine in patients with HR of 70 bpm or higher.²

2. Mechanism of action

The pacemaker I(f) current is mediated by the hyperpolarization-activated cyclic nucleotide (HCN)-gated channels, which have four isoforms in mammals. In humans, the HCN4 isoform is predominantly present in sinoatrial node cells. 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 state. Ivabradine slows HR by reducing the I(f) current-regulated diastolic depolarization in the SA node, thereby increasing diastolic duration without altering the action potential duration or causing negative inotropy.³ Ivabradine is a specific I(f) channel blocker and a selective inhibitor of the pacemaker I(f) current in the SA node.⁴

Elevated HR is known to induce myocardial ischemia in patients with CAD, and clinical evidence showed that slowing the

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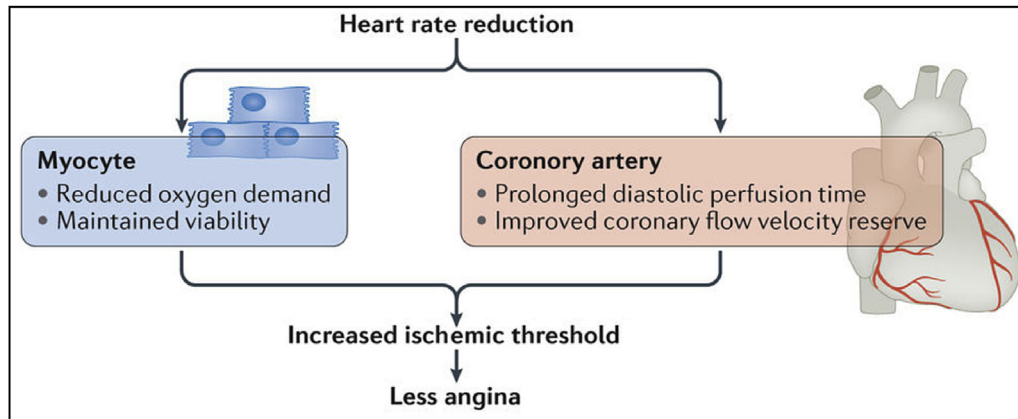


Fig. 1. Beneficial effects of heart rate reduction in angina.³

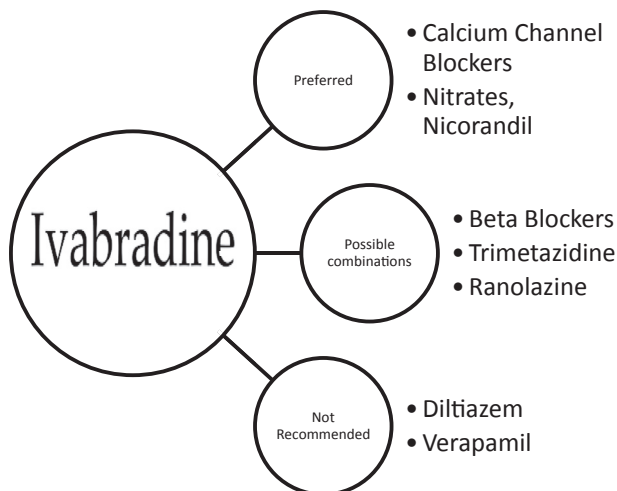


Fig. 2. Safety profile of ivabradine compared with other cardiac drugs.

HR reduces the symptoms of angina by improving microcirculation and coronary flow. Increased HR increases stroke volume, which is considered to be a compensatory mechanism. However, prolonged neuroendocrine activation resulting in depletion of catecholamines in failing myocytes has negative effects on the heart leading to hypertrophy and apoptosis which in turn causes left ventricular negative remodeling resulting in reduction in left ventricular ejection fraction (LVEF).⁴ In the oral dose range from 0.5 to 24 mg, HR is reduced almost linearly but nonlinearly at higher doses with reduced HR reaching a plateau.⁵

2.1. Pharmacokinetics

After oral administration, ivabradine reaches the maximum concentration in about 1 h and has elimination half-life of about 2 h. The absolute bioavailability of oral film-coated tablets is 40%. Cytochrome P4503A4 is involved in the metabolism of ivabradine; therefore, concurrent administration of CYP3A4 inhibitors (azole antifungals, macrolides, HIV-protease inhibitors, and so forth) should be avoided.⁵ Metabolites of ivabradine are eliminated through urine and feces.⁶ Caution is required in patients with creatinine clearance below 15 ml/min. It is contraindicated in patients with severe liver insufficiency.⁵

3. Role of ivabradine in different cardiovascular diseases

3.1. Ivabradine in HF

HR reduction with beta-blockers is known to improve the outcomes in patients with HF, partly by reducing and even reversing the progression of left ventricular remodeling. Paradoxically, long-term beta-blockade in the setting of HF exerts positive inotropism despite the well-known negative inotropic action of beta-blockers.⁴ This beneficial effect of beta-blockers may be partially related to the protection of the heart and other organs from catecholamines that may contribute significantly to the effects of these drugs. Effects of selective HR reduction could be explained by three major actions. First, HR is linearly related to myocardial oxygen consumption; second, the decrease in HR prolongs the duration of diastole and thereby supports diastolic filling and coronary blood flow; third, force-frequency relationship is inverted in HF, an increase in HR increases contractile performance in the nonfailing myocardium, whereas it is associated with a decline in contractile function in the failing myocardium. When the HR is high, the time available for diastolic calcium accumulation into the sarcoplasmic reticulum is short resulting in calcium depletion.⁷

The Systolic Heart Failure Treatment With the I(f) Inhibitor Ivabradine Trial (SHIFT) provided evidence that ivabradine can reduce hospitalizations, which sets the stage for more trials to prove or refute this hypothesis. There are fewer drug interactions associated with ivabradine, and serum drug level monitoring is not required. Ivabradine has been compared with digoxin in the SHIFT and the Digitalis Intervention Group (DIG) trial. These trials inferred that ivabradine is a more potent bradycardiac agent. However, in the DIG trial, there were more adverse events associated with digoxin. In summary, ivabradine is appealing with respect to its ability to reduce hospitalizations in patients with HF as well as its ease of dosing and monitoring.⁸

The SHIFT⁹ included only patients with HF (classes II to IV), LVEF $\leq 35\%$, sinus rhythm, and a HR ≥ 70 bpm. This trial involved 6505 patients from 677 centers who were followed up for a median duration of 22.9 months. Patients needed to be on optimal standard medical treatment for at least 4 weeks. The starting dose of ivabradine was 5 mg b.i.d. After a 14-day titration period, the 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 if 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 CV death or hospital admissions for worsening HF (primary end point) by 18%

compared with placebo ($p < 0.0001$), while hospitalizations and deaths due to HF both were reduced by 26%. The effect was consistent across all the subgroups, although it did not reach statistical significance.

A pooled analysis of the results of both the SHIFT and the Morbidity-Mortality Evaluation of the I(f) Inhibitor Ivabradine in Patients With Coronary Disease and Left Ventricular Dysfunction (BEAUTIFUL) trial¹⁰ ($n = 11,897$) with a baseline HR of ≥ 70 bpm revealed mean HR at baseline was 79.6 ± 9.2 bpm, and the mean EF was $30.3 \pm 5.6\%$ with no significant differences between treatment groups. There was a 13% relative risk reduction in CV mortality or hospitalization for HF ($p < 0.001$). Significant risk reduction was also observed for the composite outcomes of CV mortality, HF hospitalizations, or myocardial infarctions (MIs). 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 and across the spectrum of LVEFs and NYHA classes.

A post hoc study of the SHIFT¹¹ ($n = 712$) showed that patients with severe HF had poorer outcomes compared with patients with less severe HF ($n = 5973$), and those with higher HR showed better response. Among 272 patients with severe HF and a HR ≥ 75 bpm, 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% ($p = 0.034$).

A prospective cohort study¹² ($n = 767$) among patients with chronic HF receiving ivabradine twice daily reported 90% receiving it after a mean duration of 11.2 months. The result suggested that the therapy is effective and well tolerated with significant improvement in the quality of life. Compared with baseline, treatment resulted in reduced HR by 16 bpm, which was associated with a lesser decompensation rate. There was also reduction in the hospitalization rate (23% before treatment vs 5% with therapy).

Concomitant use of beta-blockers with ivabradine is common in clinical practice. Combined therapy is effective and well tolerated and results in significant benefits including improved quality of life among patients with chronic HF. In a long-term study ($n = 767$), beta-blocker therapy was prescribed in 65% of patients.¹²

An analysis of the SHIFT database showed ivabradine with $<50\%$ of target beta-blocker dose significantly reduces hospitalization due to HF.¹³

An Indian study ($n = 187$) suggested that addition of ivabradine to standard therapy in patients with dilated cardiomyopathy and symptomatic HF with targeting a HR of less than 70 bpm results in improvement of symptoms, quality of life, and echocardiographic parameters.¹⁴

In the SHIFT population, coprescription of carvedilol with ivabradine showed improvements in cardiovascular outcomes in patients with systolic HF.¹⁵

3.1.1. Ivabradine in acute HF

HR is an important therapeutic target in acute and chronic HF.¹⁶ With the same principle of myocardial stress with tachycardia, reduction in the HR may provide benefits in patients with acute HF. With this objective, use of ivabradine has been evaluated in acute HF.^{17,18} Ivabradine decreases the HR without increasing cardiac contractility. It is cardioprotective in the failing heart. Some of the beneficial effects of ivabradine may be related to downregulation of inflammatory cytokines.¹⁹

In a retrospective study ($n = 29$), the use of ivabradine on patients with sinus rhythm and a HR of more than 70 bpm and initiation of ivabradine during hospitalization was well tolerated.¹⁸ In another small study ($n = 10$) among patients with acute decompensated

systolic HF and a resting HR above 70 bpm, oral ivabradine was effective and well tolerated in reducing the HR.²⁰ In a randomized study involving patients with acute decompensated HF ($n = 58$), ivabradine prevented dobutamine-induced rise in the HR.²¹

Early administration of ivabradine plus beta-blockers is possible and well tolerated. A randomized study ($n = 71$) reported a significant reduction in the HR at 28 days and at 4 months after hospital discharge with ivabradine plus beta-blocker given during hospital admission for acute HF and reduced LVEF.²² One-year follow-up also showed that coadministration of beta-blocker and ivabradine during hospital admission is possible and safe.²³

Case reports on young men with acute HF due to myocarditis suggest a beneficial role of ivabradine in supporting hemodynamic stabilization due to HR reduction.²⁴

In a randomized, double-blind, placebo-controlled study ($n = 116$) among children with dilated cardiomyopathy with stable chronic heart failure (CHF) and 12 months of follow-up, ivabradine was significantly effective in achieving primary end point (70% vs 12%; odds ratio 17.24; $p < 0.0001$). There was a significant increase in LVEF with ivabradine as compared with placebo (13.5% vs. 6.9%; $p = 0.024$). Safety profile was similar to that of placebo.²⁵

In summary, based on the available evidence, it is clear that an adequate decrease in the resting HR should be one of the major targets in patients with HF. The preferred target should be 60 bpm or less. Beta-blockers are the drugs of choice for this purpose, but achievement of this target may not be possible with beta-blockers alone. In such cases, addition of ivabradine could be a safe and effective option.²⁶ Moreover, in the clinical practice, it is often observed that many patients are unable to take recommended doses of beta-blockers due to contraindications for their use or inability to tolerate them. In such cases too, ivabradine could be an alternative option. However, it is equally important to ensure that addition of ivabradine does not occur at the expense of a sincere attempt to prescribe and uptitrate beta-blockers to optimum doses.

3.1.2. Guideline recommendations

According to the European Society of Cardiology guidelines (2016),²⁷ ivabradine should be considered for decreasing the risk of hospitalization due to HF or cardiovascular death in symptomatic patients with LVEF of 35% or less, a sinus rhythm, and resting HR of 70 bpm and above despite treatment with beta-blockers, ACE inhibitor (or ARB), and mineralocorticoid receptor antagonist (or ARB). Ivabradine should be considered for the same indication in patients who are not able to tolerate or have contraindications to use beta-blockers. In these patients, ACE inhibitor (or ARB) and mineralocorticoid receptor antagonist (or ARB) should also be given.

For the treatment of stable angina with symptomatic HF with reduced ejection fraction, ivabradine should be considered as an antianginal agent in patients with sinus rhythm and HR of 70 bpm and above as per recommended management in combination with beta-blockers or if beta-blockers are not tolerated.

According to the 2017 focused update of the American College of Cardiology/American Heart Association and the Heart Failure Society of America guideline for the management of HF,²⁸ ivabradine can be useful for reducing hospitalization due to HF in patients with symptomatic stable chronic HF with reduced ejection fraction (i.e. LVEF of 35% or less) who are receiving guideline-based treatment including beta-blockers at a maximum tolerated dose and who are having sinus rhythm with HR of at least 70 bpm at rest.

3.2. Ivabradine in ischemic heart disease

Increased HR can provoke myocardial ischemia in patients with CAD. Reduction of HR reduces myocardial consumption of oxygen

and thereby helps to maintain its viability. Reduced HR also increases diastolic perfusion time and coronary flow reserve. These effects help to increase ischemic threshold and provide beneficial effects in patients with angina.²⁹

It was observed that the patients who received ivabradine showed an increase in central systolic blood pressure (BP) from 129 ± 22 mmHg to 140 ± 26 mmHg ($p = 0.02$), an increase of 11 mmHg, and stroke volume of 86 ± 21.8 to 107.2 ± 30.0 mL ($p = 0.002$). Changes in stroke volume and BP were not observed in the placebo group. HR is a powerful contributing factor of central BP particularly in hypertensive patients. This decrease in HR with ivabradine was associated with a significant increase in stroke volume and central systolic BP. The important finding of this study was that HR-lowering treatment with ivabradine in hypertensive stable CAD patients was further associated with increase in central systolic BP at 6-month follow-up.²⁹

A study ($n = 636$) among patients with stable angina and CAD showed that ivabradine plus beta-blocker (metoprolol) given for 4 months is effective in reducing HR, angina attacks, and improvement of quality of life. Data were recorded at baseline and at 1 month and 4 months after inclusion. Adherence was not a major concern in this study despite free combination.³⁰

In another study,³¹ Dillinger et al included 12 normotensive CAD patients with HR ≥ 70 bpm and stable status on β -blocker therapy. After 3 weeks of treatment with ivabradine, significant reduction in resting HR was observed (-15.8 ± 7.7 versus $+0.3 \pm 5.8$ bpm; $p = 0.0010$). Interestingly, the authors³¹ reported a modest increase in left ventricular ejection time ($+18.5 \pm 17.8$ versus $+2.8 \pm 19.3$ ms; $p = 0.074$) and a prolongation of diastolic perfusion time ($+215.6 \pm 105.3$ versus -3.0 ± 55.8 ms with placebo; $p = 0.0005$). They concluded that HR reduction with ivabradine does not increase central BP in normotensive stable CAD patients and is associated with improvement in myocardial perfusion index/time.

The BEAUTIFUL trial³² was a multinational randomized trial assessing the effect of ivabradine on mortality and morbidity in 10,917 patients with stable CAD with LVEF $<40\%$, sinus rhythm, and HR ≥ 60 bpm. The starting dose of ivabradine (and matched placebo) was 5 mg b.i.d, and the dose was uptitrated to 7.5 mg b.i.d in 2 weeks in those with HR ≥ 60 bpm, and the dose was maintained at 5 mg b.i.d. if HR was <50 bpm or if they had signs or symptoms related to bradycardia. Although ivabradine did not reduce the primary composite end point of CV death or admissions to hospital for MI or new-onset or worsening HF, but the drug reduced the incidence of the secondary end points of fatal and nonfatal MI in patients with a baseline HR ≥ 70 bpm.

Ivabradine is an antianginal agent because it decreases HR without a negative inotropic effect without a coronary vasoconstrictor effect. Ivabradine increases diastolic duration and coronary blood flow and preserves coronary dilation during exercise. In addition, it increases coronary flow reserve and improves collateral perfusion. These properties make ivabradine an effective antianginal and anti-ischemic agent in patients with CAD.³³ Ivabradine gives more symptomatic relief and also results in increase in ejection fraction compared with doubling the dose of β -blockers in patients with HF.^{34,35} In the Study Assessing the Morbidity-Mortality Benefits of the I(f) Inhibitor Ivabradine in Patients with Coronary Artery Disease (SIGNIFY) trial, a major trial³⁶ assessing the morbidity and mortality benefits of ivabradine, 19,102 stable CAD patients were recruited. These patients showed presence of additional CV risk factors and resting HR ≥ 70 bpm. Investigators of the SIGNIFY trial enrolled patients without any symptoms of HF or LV systolic dysfunction with a mean baseline LVEF of $56.5 \pm 8.6\%$. Enrolled patients received guideline-based standard therapy. In these stable CAD patients, ivabradine was found to have no effect on the primary end point of composite CV death or nonfatal MI

with an annual event rates of 3.0% with ivabradine and 2.8% with placebo [hazard ratio (HR) 1.08, 95% confidence interval, 0.96–1.20, $p = 0.20$]. Furthermore, there was no significant difference between the ivabradine and placebo groups with regard to secondary end points such as cardiovascular deaths (HR 1.10, $p = 0.25$), nonfatal MI (HR 1.04, $p = 0.60$), or all-cause mortality (HR 1.06, $p = 0.35$). Results of the SIGNIFY trial are in sharp contrast with those of the SHIFT, which included a completely different patient population with symptomatic HF of ischemic and nonischemic origin. These results raise an important question regarding the relationship between elevated HR and outcomes in cardiovascular disease.^{8,36}

The Heart Rate Reduction by Ivabradine for Improvement of Endothelial Function in Patients with CAD (RIVENDEL) study evaluated the effect of ivabradine on endothelial function in patients with CAD ($n = 70$). In this randomized study, patients in 1 group ($n = 36$) received ivabradine 5–7.5 mg b.i.d after 30 days of percutaneous coronary intervention (PCI) while others ($n = 34$) received standard medical treatment. Over the 8-week study period, there was a significant reduction in the HR and improvement in nitroglycerin-mediated dilatation ($p < 0.001$). The results suggested that addition of ivabradine to standard medical care improves endothelial function in patients with CAD undergoing revascularization by PCI.³⁷

3.2.1. Role of ivabradine in CHD

Reduction in the HR in patients with CHD may help to decrease risk of myocardial ischemia. Considering the available data, ivabradine plays a significant role in patients with CHD. Ivabradine does not have any effect on the respiratory parameters. It can be useful agents for elderly patients and those with diabetes or asthma for whom other antianginal agents (beta-blockers) are relatively contraindicated.³⁸

3.2.2. Ivabradine dosage schedule for treatment of angina and HF

It is recommended that the decision to initiate or titrating the dose should be done using HR measurements. The starting dose of ivabradine should not exceed 5 mg b.i.d with meals in patients aged below 75 years. After 3–4 weeks of treatment, if the patient continues to be symptomatic, if the initial dose is well tolerated, and if resting HR remains above 60 bpm, the dose may be increased to 7.5 mg twice daily.

The dose can be decreased to 2.5 mg BD if resting HR is below 50 bpm or if associated with symptoms related to bradycardia.

3.3. Use of ivabradine pretreatment before coronary computed tomography angiography

Beta-blockers are commonly used for reducing HR in patients undergoing coronary computed tomography angiography (CTCA). In many patients, despite beta-blockers, HR remains above the target of 65 bpm.³⁹ Reduction in the HR is important for better image quality and diagnostic accuracy of CTCA.⁴⁰

Premedication with ivabradine reduces the HR and improves the image quality of CTCA.⁴¹ Ivabradine has shown to be safe and effective in controlling HR before performing CTCA and thereby reducing the need for additional intravenous beta-blockade.^{40,42} A retrospective study showed that pretreatment with ivabradine taken at home for only 1 day can result in significantly reduced HR and lower requirement of intravenous beta-blockers.⁴³ A comparative study ($n = 100$) has shown ivabradine to be significantly more effective than metoprolol in reducing HR of patients undergoing CTCA. The percentage reduction in HR with two agents was 23.89% vs 15.20% ($p = 0.0001$). Ivabradine did not reduce BP, whereas metoprolol did.³⁹ A prospective study ($n = 259$) among patients referred for CTCA reported that with ivabradine 7.5 mg, more

number of patients referred for CTCA achieve target HR than with ivabradine 5 mg.⁴⁴ Another prospective, randomized study ($n = 101$) showed that 7-day premedication with ivabradine is effective in reducing HR in patients undergoing CCTA. Ivabradine use also reduces the need for beta-blockers for lowering the HR and also the need for antianxiety medicine.⁴⁵ A meta-analysis of randomized controlled trials showed that pretreatment with ivabradine is significantly more effective in improving HR of patients achieving the target HR during CTCA. Compared with beta-blockers, ivabradine showed significant effect on HR reduction during CTCA. Ivabradine also showed significant reduction in HR before CTCA without significant effect on BP.⁴⁶ Overall, these studies suggest that ivabradine is an attractive option for reducing HR in patients undergoing CTCA. In addition to proven efficacy and safety, ivabradine does not significantly affect BP, offering an edge of advantage over beta-blockers.

3.4. Other potential uses of ivabradine

3.4.1. Chronic obstructive pulmonary disease and asthma

Increased sympathetic activity and use of bronchodilators may cause tachycardia and have adverse effects on the functional capacity in patients with chronic obstructive pulmonary disease (COPD).⁴⁷ Using beta-blockers in patients with COPD has limitations due to the risk of bronchoconstriction.⁴⁸ Moreover, in many patients, HF and COPD may coexist, and it can result in poor prognosis. In such cases, ivabradine can be an effective and safe option for use in patients with chronic HF with or without COPD. It can also be combined with beta-blockers.⁴⁹ A randomized, placebo-controlled trial ($n = 80$) among patients with COPD having HR of 90 bpm or higher showed a significant improvement in 6-min walk distance with 2-week treatment of ivabradine 7.5 mg twice daily. This was associated with significant improvement of dyspnea.⁴⁷

A randomized, double-blind, crossover study among patients with asthma and COPD ($n = 40$) showed that ivabradine is significantly more effective in reducing HR than placebo. Ivabradine was well tolerated. The results suggest that ivabradine can be a good alternative for reducing HR in patients with respiratory disease and in those who cannot be given beta-blockers.⁴⁸

Ivabradine can be a useful option for the prevention of increase in the HR after salbutamol inhalation in patients with COPD with coexisting CHD.⁵⁰ It can also be useful in the treatment of angina pectoris and CHF in patients with CHD with COPD.⁵¹

Ivabradine can be added to bisoprolol in patients with ischemic heart disease with COPD, if required.⁵² Combination of bisoprolol and ivabradine is safe and effective for reducing HR with advantages of better antianginal effect, less need of broncholytic therapy, and reduced hospitalizations as compared with bisoprolol alone in patients with stable angina and COPD.⁵³

Similarly, a double-blind, placebo-controlled, crossover study ($n = 20$) has shown that ivabradine does not have any effect on respiratory function or symptoms in patients with asthma.⁵⁴ Ivabradine can be an effective alternative to beta-blockers as an antianginal agent for patients with cardiorespiratory pathology.⁵⁵

3.4.2. Pulmonary hypertension

The other potential use of ivabradine is for pulmonary arterial hypertension.^{56,57} In an experimental study, HR reduction using ivabradine in animals with pulmonary hypertension showed improvement in biventricular filling and hemodynamics. Thus, improved interactions between two ventricles and ventricular cycle events with ivabradine can have beneficial effects on pulmonary hypertension.⁵⁸ At the moment, there are limited data on the use of ivabradine for pulmonary arterial hypertension in large well-designed clinical trials. In a comparative clinical trial ($n = 60$),

ivabradine 10 mg per day given for 2 weeks has been shown to be effective in reducing pulmonary hypertension and HR with improvement in exercise tolerance in patients with COPD.⁵⁹

3.4.3. Sepsis and multiple organ dysfunction syndrome

Sepsis often results in multiple organ dysfunction syndrome. Persistent tachycardia in these patients can have a deleterious effect. Reduction of HR may be useful in improving survival in such cases.⁶⁰ The effects of ivabradine in patients with multiple organ dysfunction syndrome has been studied.⁶¹ Experimental research suggests the beneficial effects of ivabradine on endothelial cell function. A murine model of abdominal sepsis showed the potential of ivabradine in improving microvascular derangements and reduced organ dysfunction.⁶² Some evidence indicated that I(i) blocking potency is preserved under raised endotoxin levels in human atrial myocytes.⁶⁰ Because of the reduced pacemaker activity and decreased HR, ivabradine allows more blood flow to the myocardium.⁶ There is some controversial evidence too. The results of a randomized trial in an experimental model of septic shock suggest that isolated HR reduction by ivabradine is not associated with the beneficial effect on cardiac or vascular functions.⁶³

In a prospective, randomized study ($n = 70$), patients with multiple organ dysfunction syndrome, a sinus rhythm, and HR of 90 bpm or higher and contraindications to β -blocker therapy were treated with standard treatment or standard treatment plus ivabradine (5 mg b.i.d) for 96 h. After treatment, there was a reduction in the median HR by 16 bpm with ivabradine as compared with 7 bpm in the control group ($p = 0.014$).⁶⁴

3.4.4. Other cardiac conditions

In a small study ($n = 18$) with 6-month follow-up, Calo et al⁶⁵ reported a significant reduction in the HR in patients with inappropriate sinus tachycardia. Results of stress test suggested improved physical tolerance. These results suggest the potential for the use of ivabradine as an alternative to calcium channel blockers or beta-blockers in these patients. Most of the patients with this condition are females; hence, teratogenic potential of ivabradine should be considered. A pooled analysis of the nine prospective studies ($n = 145$) showed effectiveness of ivabradine in reducing HR and symptoms in patients with inappropriate sinus tachycardia without structural cardiac problem. Well-designed, large comparative clinical trials on the effects of beta-blockers are required to confirm the results.⁶⁶

In a retrospective study, Ruzieh et al⁶⁷ reported the effects of ivabradine-based treatment in patients with postural tachycardia syndrome (POTS) ($n = 49$). About 78% of the patients in this study reported a significant improvement without any major adverse event, suggesting its role in POTS. In another small study ($n = 22$) among children aged between 11 and 17 years, ivabradine resulted in reduction in HR. Symptom improvement was seen in 68% patients. The study results proved effectiveness and safety of ivabradine in children with POTS.⁶⁸

Although great care has been taken to include all important studies and evidence on the effect of ivabradine on different cardiovascular diseases because of the evolving and dynamic field of clinical research, the possibility of missing some studies cannot be ruled out.

4. Safety of ivabradine

The most common adverse events associated with ivabradine are bradycardia, atrial fibrillation, phosphenes (luminous phenomena), and hypertension. Postmarketing survey revealed that ivabradine was associated with rash, diplopia, angioedema, pruritus, urticaria, visual impairment, erythema, and vertigo. Therefore,

ivabradine should not be started in patients with an HR lower than 70 bpm and in those with second-degree atrioventricular block. Ivabradine should not be given during pregnancy because it exhibits reproductive toxicity in animal studies (Pregnancy Category C). In the BEAUTIFUL trial³² bradycardia was a major adverse event in the ivabradine group needing discontinuation of the drug in some cases (13% vs 2% placebo). There was a safety concern regarding the increased risk of cardiovascular death in the ivabradine group but the difference was insignificant risk being higher in those with an HR less than 70 bpm. The SHIFT⁹ revealed that the incidence of serious side effects was lower in the ivabradine group compared with the placebo group (45% vs 48%, $p = 0.025$). Bradycardia was the most common adverse event that led to discontinuation in 48 (1%) patients in the ivabradine group and 10 (<1%) patients in the placebo group.

Ivabradine can be combined with calcium channel blockers, nitrates, nicorandil, beta-blockers, trimetazidine, or ranolazine, but combining it with diltiazem or verapamil is not recommended.

Ivabradine should be avoided in patients with known hypersensitivity to active ingredients of the formulation or excipients. The other contraindications for use of ivabradine include bradycardia, i.e. HR less than 60 bpm before the initiation of the treatment, cardiogenic shock, acute MI, hypotension (BP less than 90/50 mmHg), sick sinus syndrome, unstable angina, and third-degree atrioventricular block. The drug should also be avoided in pregnant and lactating women.⁵

5. Conclusion

Increased HR produces adverse impact on myocardium. Beta-blockers are effective agents for reducing HR, but in many patients, HR reduction is not achieved only with beta-blockers. In addition, in some patients, beta-blockers may not be used due to contraindication or intolerance. In patients with HF, beta-blockers can reduce hospitalization and result in a significant improvement in the quality of life. Several studies suggest that ivabradine is an attractive, effective, and safe choice in patients with HF. HR reduction using ivabradine is similar to that of beta-blockers. Ivabradine provides additional benefits when used in combination with the other antianginal drugs such as beta-blockers (except diltiazem and verapamil). In symptomatic patients, despite treatment with beta-blockers, adding ivabradine provides a significant benefit. Future studies with newer indications can support the clinicians to increase their confidence in the use of ivabradine.

Conflicts of interest

All authors have none to declare.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.ihj.2018.08.008>.

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