Ivabradine: a new rate-limiting therapy for coronary artery disease and heart failure

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***Abstract*:** Ivabradine is a new bradycardic agent acting on the I_f channels of sinoatrial nodal cells to decrease the rate of diastolic depolarization and thus heart rate. The benefit of ivabradine over other negatively chronotropic agents is its absence of negative inotropy. Effective management of coronary artery disease, in terms of reducing morbidity and mortality, is reliant on controlling heart rate. Ivabradine has been shown to safely and effectively reduce heart rate without compromising cardiac function in patients with coronary artery disease and more recently in patients with heart failure and raised heart rate. Furthermore, ivabradine has been shown to have a favourable side-effect profile compared with alternative bradycardic agents. This article reviews the evidence for ivabradine in coronary artery disease and heart failure and compares its safety with alternative bradycardic agents for these conditions.

***Keywords*:** coronary artery disease, drug safety, I_f channel, I_f channel inhibitor, ivabradine

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Introduction

Ivabradine is a new therapeutic agent designed to reduce heart rate at rest and during exercise by selective inhibition of a novel receptor (I_f channel) located on the pacemaker-cell membrane within the sinoatrial node. As such, ivabradine joins a list of rate-limiting medications already available to prescribers for the control of heart rate in coronary artery disease (CAD). This review gives a brief overview of the physiological benefits of heart rate reduction in CAD and heart failure. The pharmacology of ivabradine and the physiological and clinical impact of inhibition of the I_f channel are reviewed. The results of recent clinical trials of ivabradine are also discussed giving context to the current location of ivabradine in treatment schedules for CAD and heart failure. In addition, ivabradine is reviewed in terms of its safety, and in relation to other rate-limiting medications.

Physiological principles of heart rate reduction in coronary artery disease and heart failure

The risk of cardiovascular mortality due to increased heart rate has been investigated in a large observational study of 24,913 patients with CAD [Diaz *et al.* 2005]. Patients with a baseline heart rate of at least 83 beats/min (bpm) were found to have a significantly higher risk of cardiovascular mortality [hazard ratio (HR) = 1.31; 95% confidence interval (CI) = 1.15–1.48; $p < 0.001$]. Patients with CAD and controlled heart rate were found to have a lower risk of cardiovascular mortality.

The principal symptom of CAD is chest pain due to myocardial demand for oxygen being in excess of physiological supply. In patients with CAD, this is characteristically because of the presence of atheroma causing stenosis of the coronary arteries. Decreasing heart rate allows the heart to function more effectively by increasing diastole, increasing coronary perfusion and allowing complete ventricular filling and therefore an increase in cardiac efficiency. Plaque rupture is a potentially fatal consequence of CAD and the risk is increased at higher heart rate because of haemodynamic stress. By controlling heart rate the risk of plaque rupture, and subsequent ischaemia, may be reduced. In patients with heart failure, lowering the heart rate with β-blockers is standard treatment resulting in significant mortality benefits in this patient group.

Until recent years there were two main types of heart rate limiting medication classes prescribed for patients with CAD – β-blockers and nondihydropyridine rate-limiting calcium channel blockers. The emergence of ivabradine

offers an exciting alternative bradycardic agent in terms of efficacy and safety.

Physiology of action potentials and the role of the I_f channel

The sinoatrial node is composed of autonomous pacemaker cells. Because of sequential ionic movements across the cell membrane, via four separate channels, these cells cause an action potential to be generated which is then conducted across the heart, ultimately resulting in coordinated muscle contraction [Bois *et al.* 1996]. The I_f channel is made up of hyperpolarisation-activated, cyclic nucleotide gated channel subunits. The morphology of the cardiac I_f channel is similar to I_h channels found in neuronal cells [Bucchi *et al.* 2002]. Ivabradine blocks the I_f channel when the channel gate is open [Bucchi *et al.* 2007]. The I_f channel is activated at between −40 and −50 mV, which relates to an influx of both Na^+ and K^+ ions [Bucchi *et al.* 2002]. The opening of the I_f channel is dependent on both voltage and cyclic adenosine monophosphate (cAMP) intracellular concentration. When cAMP is bound to the I_f channel there is a higher likelihood of it being open, therefore allowing ivabradine binding. Adrenergic stimulation (e.g. sympathetic nervous system) increases cAMP concentration and hence binding to the I_f channel; the opposite is true in the presence of cholinergic stimulation (e.g. parasympathetic nervous system) [Sulfi and Timmis, 2006]. Pacemaker activity is spontaneously generated by the I_f current in the pacemaker cells of the sinoatrial node [Borer, 2004]. However, the rate of this activity can be influenced by external factors, including medication, hormones and sympathetic nerve activity [Scott *et al.* 2009].

Figure 1 shows an action potential generated by a sinoatrial nodal cell. Each separate phase of the action potential relates to the opening, closing or both of different ion channels in the sinoatrial node. Figure 2 shows the effect ivabradine has on the action potential.

Pharmacology of ivabradine

Ivabradine is absorbed quickly and almost completely via the oral route. Peak plasma concentrations are seen after 2 h if taken with food [Sweetman, 2009]. Ivabradine is known to be plasma protein bound (~70%) and undergoes extensive hepatic metabolism [Sweetman, 2009]. This produces at least four metabolites when administered *in vivo*, including two metabolites with only minor variations in structure

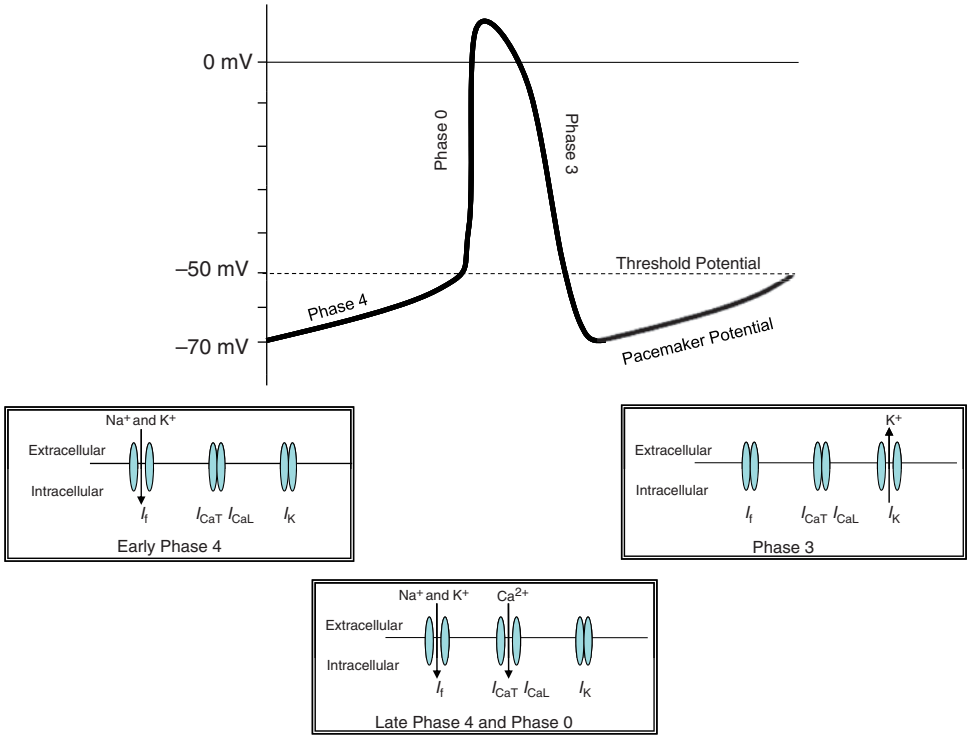

Figure 1. Sinoatrial ion channel activity and the generation of an action potential.

compared with the parent drug: *O*- and *N*-demethylated metabolites [Francois-Bouchard *et al.* 2000; Klippert *et al.* 1998]. The *N*-demethylated metabolite is known to contribute to the pharmacological effect of the parent drug [Ragueneau *et al.* 1997] and is thought to be the main active metabolite [Portoles *et al.* 2006]. Metabolism occurs via the cytochrome P450 3A4 (CYP3A4) pathway; however, interaction between ivabradine and other inhibitors of the CYP3A4 enzyme does not appear to significantly affect the efficacy of ivabradine [Portoles *et al.* 2006]. Combination with strong CYP3A4 inhibitors such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin), and HIV protease inhibitors is contraindicated. The combination of ivabradine with diltiazem or verapamil (moderate CYP3A4 inhibitors) results in an increase in ivabradine exposure (two to threefold increase in the area under the curve) and an additional heart rate reduction of 5 bpm. The concomitant use of ivabradine with these medications, although unlikely to cause significant clinical harm, is not recommended. Ivabradine has an elimination half life of 2 h [Sweetman, 2009]. In a dose-ranging study, ivabradine was shown to have a dose-dependent rate-limiting activity [Ragueneau *et al.* 1997]. In another study investigating potential electrophysiological alterations after ivabradine intravenous administration, ivabradine was shown to slightly increase the QT interval [Camm and Lau, 2003]. Table 1 provides a comparison of some of the key differences between ivabradine and β-blockers.

Clinical efficacy data

Dose ranging and efficacy

Ivabradine is the first I_f current inhibitor to be clinically useful at reducing heart rate. This clinical benefit was first tested for efficacy in a cohort of 360 patients with stable angina [Borer *et al.* 2003]. This dose-ranging study tested doses of 2.5 mg, 5 mg and 10 mg of ivabradine or placebo twice daily over 2 weeks. A 3-month extension period then investigated the effect of titration to 10 mg of ivabradine twice daily. After 2 weeks, mean time to ST-segment depression was significantly increased in the group receiving 5 mg of ivabradine twice daily (44.1 s *versus* 9 s; $p = 0.016$), signifying an improvement in exercise tolerance and anti-ischaemic benefit in a dose-dependent fashion. Key clinical trials are reported in Table 2 and discussed below.

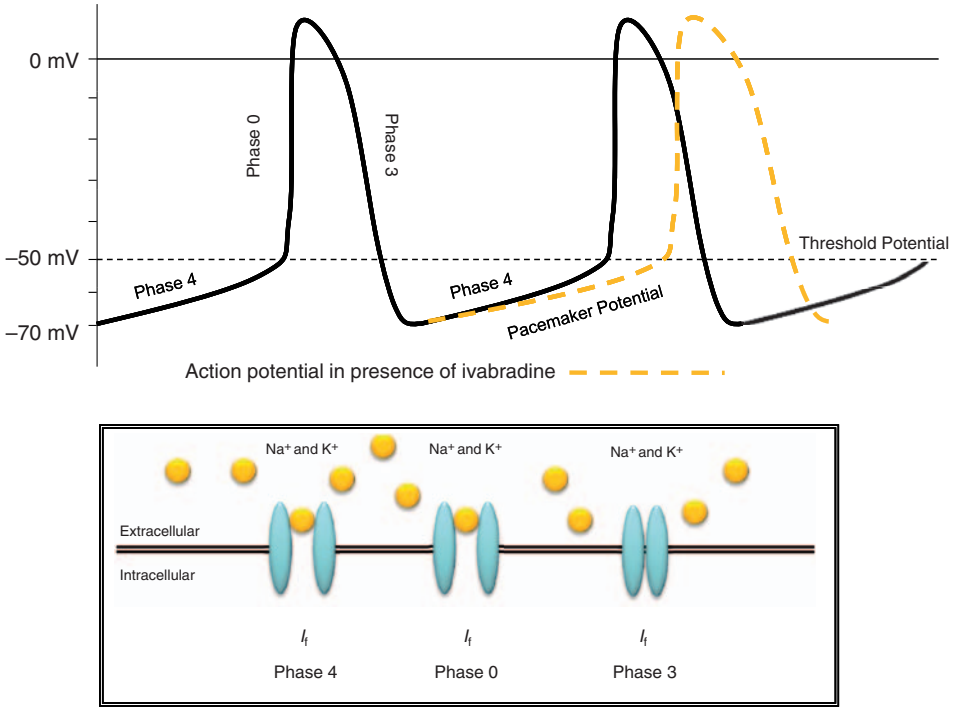

Figure 2. Pharmacodynamic I_f channel interaction and the effect on the sinoatrial action potential.

Table 1. Comparison of cardiovascular effects and side effects of ivabradine and β-blockers.

Medication	Mortality	Exercise-induced ST shift	Cardiac contractility	Peripheral vasoconstriction	Respiratory effects
β-blockers	Decrease	Time to shift prolonged	Decrease	Yes	Yes – causing wheeze
Ivabradine	Decrease	Time to shift prolonged	No effect	No effect	No effect

Table 2. Common side effects and their reported incidence from clinical trials.

Trial	Drug regimen	Bradycardia	Eye disorders including phosphenes
INITIATIVE	Ivabradine *versus* atenolol	2.2% (7.5 mg twice daily) and 5.4% (10 mg twice daily) *versus* 4.3% atenolol (p = NA)	5 withdrawals in the ivabradine group *versus* none in the atenolol group (p = NA)
ASSOCIATE	Ivabradine *versus* placebo	19 (4.2%) *versus* 2 (0.5%) (p = NA)	9 (2%) *versus* 4 (0.9%) (p = NA)
BEAUTIFUL	Ivabradine *versus* placebo	149 (6%) *versus* 21 (1%)* (p = NA)	21 (0.4%) *versus* 12 (0.2%)* (p = NA)
SHIFT	Ivabradine *versus* placebo	150 (5%) *versus* 32 (1%)[$], 184 (6%) *versus* 48(1%)[‡] (both $p < 0.0001$)	89 (3%) *versus* 17 (1%) ($p < 0.0001$)

*Dropout rates – no reports of total incidence.
[$]Symptomatic bradycardia.
[‡]Asymptomatic bradycardia.
NA, not available/reported.

Comparison against other antianginal agents

On the premise of the results found by Borer and colleagues [Borer *et al*. 2003] a trial was designed to test the 5 mg twice daily dose of ivabradine *versus* atenolol using a noninferiority design [Tardif *et al.* 2005]. The INITIATIVE trial investigated 939 patients with stable angina who were randomised to receive ivabradine 5 mg twice daily for 4 weeks then either 7.5 mg or 10 mg twice daily for a further 12 weeks, or atenolol 50 mg daily for 4 weeks before titration to 100 mg for a further 12 weeks. The primary endpoint of the study was exercise tolerance at month 1 and 4. Ivabradine was shown, at all doses, to be noninferior (86.8 ± 129.0 s, 91.7 ± 118.8 s, 78.8 ± 133.4 s for ivabradine 7.5 mg twice daily, 10 mg twice daily and atenolol 100 mg daily respectively; $p < 0.001$) to atenolol for increasing exercise tolerance. Episodes of angina were decreased by two-thirds in all groups.

The antianginal efficacy of ivabradine has also been tested against another antianginal drug, amlodipine [Ruzyllo *et al.* 2007]. Again, a double-blind parallel group design was employed to randomise 1195 patients with chronic stable angina to treatment with ivabradine 7.5 mg twice daily, ivabradine 10 mg twice daily or amlodipine 10 mg daily. The primary endpoint was the change in exercise tolerance seen at monthly intervals. Ivabradine was shown to have comparable anti-ischaemic ability to amlodipine at 3 months when exercise tolerance was improved by 27.6 ± 91.7 s, 21.7 ± 94.5 s and 31.2 ± 92.0 s for ivabradine 7.5 mg twice daily, ivabradine 10 mg twice daily and amlodipine 10 mg daily respectively (noninferiority $p < 0.001$). Again, in line with the results of the INITATIVE trial, episodes of angina were decreased in all the groups. No significant difference was seen between the groups.

Combination with other antianginal agents

A meta-analysis has shown that the combination of a calcium channel antagonist and a β-blocker is more effective at increasing exercise tolerance than either medication as monotherapy [Klein *et al.* 2002]. This dual approach to CAD management was investigated recently in the ASSOCIATE study in which the efficacy and tolerability of a combination of ivabradine and atenolol were studied [Tardif *et al.* 2009]. The trial used a randomised, double-blind design in 889 patients with chronic stable angina who were on atenolol 50 mg daily. They were then randomised to receive ivabradine 5 mg twice daily for 2 months titrating to 7.5 mg twice daily for a further 2 months, or placebo. The primary endpoint was again the change in exercise tolerance from baseline until the end of the study. After 4 months exercise duration in the ivabradine group was found to be 24.3 ± 65.3 s compared

with 7.7 ± 63.8 s in the placebo group ($p < 0.001$), signifying the compound effect of double antianginal therapy.

Coronary artery disease and left ventricular systolic impairment data

The largest trial investigating the efficacy of ivabradine is the BEAUTIFUL study [Fox *et al.* 2008a]. This trial investigates the potential of ivabradine to be of benefit to patients with CAD and left ventricular systolic dysfunction [Fox *et al.* 2006]. BEAUTIFUL was a randomised, double-blind, placebo-controlled, parallel-group trial in which patients randomised to the treatment arm were initialised on ivabradine 5 mg twice daily before being titrated to a target of ivabradine 7.5 mg twice daily if possible. The control group were given matching placebo in addition to appropriate cardiovascular medication. In total, 10,917 patients were randomised, the mean ejection fraction was 32% and the mean heart rate was 71.6 bpm [The BEAUTIFUL Study Group, 2008]. Eighty seven percent of patients were receiving β-blocker therapy as standard background treatment. The trial was outcome based and the primary outcome measure was a composite of cardiovascular death, acute myocardial infarction (MI) or hospitalisation for new or worsening heart failure. The trial had a median follow up of 19 months. Ivabradine did not affect the primary composite endpoint (HR = 1.00; 95% CI = 0.91–1.1; $p = 0.94$). In addition, the number of serious adverse effects in the ivabradine group was found to be lower than in the placebo group: 1233 (22.5%) *versus* 1239 (22.8%) ($p = 0.7$).

There were two main findings in the BEAUTIFUL trial. First, not all patients with CAD and left ventricular systolic impairment would benefit from the addition of ivabradine for the prevention of cardiovascular morbidity and mortality, but that a subgroup of patients with a heart rate greater than 70 bpm may benefit. Second, ivabradine at either 5 mg or 7.5 mg twice daily had a comparable side-effect profile to placebo.

The BEAUTIFUL investigators completed a subgroup analysis of the data captured from the BEAUTIFUL trial [Fox *et al.* 2008b]. In this analysis patients were grouped according to baseline heart rate as well as using heart rate as a continuous variable. The analysis found that patients with a heart rate of at least 70 bpm had a 34% ($p = 0.0041$) higher risk of cardiovascular death compared with patients with a heart rate less than 70 bpm. The investigators also found that there was a correlation between the degree to which the heart rate was higher than 70 bpm and the outcomes of mortality and heart failure related events; this correlation was found to be weaker for coronary outcomes. However, it should be emphasised that, ultimately, the primary endpoint of the BEAUTIFUL trial was negative.

The SHIFT trial was designed to compare the addition of ivabradine 7.5 mg twice daily or placebo to standard treatment, including a β-blocker, for patients with heart failure and a New York Heart Association (NYHA) classification of II–IV and ejection fractions less than 35% [Menown, 2007]. The SHIFT trial investigated the potential for ivabradine to improve cardiovascular outcomes, symptoms and quality of life in patients with heart failure and systolic dysfunction [Swedberg *et al.* 2010b]. A statistically significant reduction in the primary endpoint, a composite of cardiovascular mortality or hospital admission with worsening heart failure, was reported on the addition of ivabradine (HR = 0.82; 95% CI = 0.75–0.90; $p < 0.0001$) [Swedberg *et al.* 2010a]. However, this was mainly due to a reduced admission rate because the reduction in cardiovascular mortality alone was not statistically significant. On stratification of baseline heart rate, the greatest benefit was found in patients with an initial heart rate of at least 80 bpm [Böhm *et al.* 2010]. The major confounding factor with SHIFT, which will affect its ability to influence clinical practice, is the type of β-blocker used and the dose to which it had been titrated. Over 15% of patients received β-blockers that have no proven benefit to survival in heart failure [Teerlink, 2010]. Also, only 49% of patients reached 50% of the target β-blocker dose and only 23% of patients were at target dose [Swedberg *et al.* 2010a]. It is unclear if the benefits demonstrated in SHIFT would persist in a population of patients on an appropriate β-blocker at a target dose. What SHIFT did show was that for patients intolerant of β-blockers, ivabradine presents a potential alternative treatment option to control heart rate in heart failure.

When considering the results of both the SHIFT and BEAUTIFUL trials there would appear to be an association between the highest baseline heart rate and the greatest reduction in

cardiovascular mortality. Until now the significance of this has yet to be explored fully in a trial specifically designed to investigate a cohort of patients with tachycardia. The SIGNI_fY study will assess patients with CAD, normal left ventricular function and a resting heart rate of at least 70 bpm [Ferrari, 2009].

Safety and tolerability data

Dose comparison data

The safety of two standard doses of ivabradine was investigated as part of a long-term safety trial in 386 patients with chronic stable angina [López-Bescós *et al.* 2007]. A randomised, double-blind, parallel-group study was used to compare ivabradine 5 mg twice daily and 7.5 mg twice daily over a 12-month period. Patients were permitted to be on concomitant antianginal medication. Antianginal efficacy was also measured by monitoring the reduction in angina attacks between month 0 and 12. The number of angina attacks decreased by over 50% ($p < 0.001$) in both groups between month 0 and 12. The most commonly reported side effect was transient phosphene-like visual disturbances, which led to the withdrawal of four patients. These luminous phenomena are described as transient enhanced brightness in a limited area of the visual field and are generally mild or moderate in severity. Sinus bradycardia was reported in three patients warranting treatment withdrawal. Overall the results showed that ivabradine was tolerated well (side events 24 *versus* 32 for 5 mg and 7.5 mg doses respectively) at both doses, although there were more patients experiencing side effects at the higher dose.

Bradycardia

As might be expected from a bradycardic agent, sinus bradycardia is one of the main side effects of the medication. Bradycardia occurs in 3.3% of patients, particularly within the first 2–3 months of treatment; only 0.5% of patients experience severe bradycardia below or equal to 40 bpm. In the BEAUTIFUL study, the rate of discontinuation in the ivabradine group compared with the placebo group was 149 (6%) *versus* 21 (1%) respectively [Fox *et al.* 2008a]. Of the 149 patients who withdrew because of bradycardia, only 34 (23%) were symptomatic. Bradycardia is dose dependent but it should be noted that the effect will plateau. This is because of the number of different ionic channels contributing to pacemaker potential (potentially up to 10) so that when 100% of the I_f channels are inhibited, heart rate is only reduced by a maximum of 25–30% [DiFrancesco and Camm, 2004].

Ivabradine is contraindicated when the patient's resting heart rate is below 60 bpm prior to treatment. If, during treatment, the heart rate decreases persistently below 50 bpm at rest or the patient experiences symptoms related to bradycardia such as dizziness, fatigue or hypotension, the dose must be titrated downward, possibly to a dose of 2.5 mg twice daily (half a 5-mg tablet twice daily). Treatment should be discontinued if heart rate remains below 50 bpm or symptoms of bradycardia persist.

Cross-reactivity with I_h channels

Hyperpolarization voltage-gated channels are not exclusive to pacemaker cells in the sinoatrial node but are also found in neuronal I_h channel retinal and CNS tissues [Cervetto *et al.* 2007]. Because of the lipophobic nature of the structure of ivabradine it does not cross the blood–brain barrier. However, there is cross-reactivity of ivabradine with I_h channels in ocular tissue. This creates the presence of phosphene-like transient adverse drug reactions in 15% of patients [Savelieva and Camm, 2006]. In the largest study of ivabradine so far, BEAUTIFUL, 37 patients (0.3%) dropped out because of a composite of eye disorders, including phosphenes, blurred vision and visual disturbance [Fox *et al.* 2008a]. All symptoms disappeared on withdrawal of the study medication. Phosphene effects are reported by 14.5% of patients and are generally experienced in the first 2 months of treatment [Cervetto *et al.* 2007]. The effects are increased with increasing ivabradine dose.

Electrophysiological safety

Ivabradine affects the rate of ventricular repolarisation, potentially due to a weak inhibitory effect on I_{Kr} channels [Savelieva and Camm, 2008]. This effect prolongs the repolarisation (QT interval) by no more than 2 ms, which is within the recommended guidelines for QT/QTc prolongation due to torsadogenic potential [Savelieva and Camm, 2006]. Perhaps more importantly, however, ivabradine should not be prescribed with other medications that can prolong the QT interval (e.g. sotalol or amiodarone). Ivabradine must also be avoided in patients with sick sinus syndrome because of the pharmacodynamic interactions within the sinoatrial node [Savelieva and Camm, 2006]. In contrast to β-blockers, ivabradine has no

affect on conduction in the atrioventricular node and therefore is of no clinical benefit in the treatment of atrial fibrillation [Nixon *et al.* 2008].

Safety comparison with other bradycardic agents

Ivabradine is a negatively chronotropic agent without any significant negatively inotropic effect, unlike β-blockers [Klippert *et al.* 1998; Bois *et al.* 1996]. Another potential benefit of ivabradine is the lack of vasoconstriction which can cause a symptomatic decrease in distal perfusion in patients taking β-blockers [Savelieva and Camm, 2006]. In a small trial of patients with asthma, ivabradine was found to have no significant effect on respiratory function or wheeze [Babu *et al.* 2008]. Due to extensive experience of using β-blockers to treat CAD, and because they are relatively cheap in comparison to other bradycardic agents, it is unlikely that ivabradine will be used as a first-line agent unless patients are intolerant to β-blockers or there are contraindications [Begg, 2008]. One of the main adverse effects of β-blockers, even in patients who tolerate treatment well, is rebound tachycardia and hypertension. The potential for rebound tachycardia with ivabradine has been investigated and there appears to be no evidence of this effect [Borer and Le Heuzey, 2008], which is an obvious benefit for ivabradine compared with β-blockers.

Pooled safety data

A pooled subpopulation analysis using the data generated from five large randomised trials in a total of 2425 patients with angina pectoris has confirmed that ivabradine is well tolerated and that adverse drug reactions are rare [Tendera *et al.* 2009]. The dropout rate due to new-onset adverse drug reactions in all subgroups was less than 1.5%.

Other clinical considerations

The use of ivabradine is restricted to patients in sinus rhythm. One clinical concern is when patients who are prescribed ivabradine monotherapy as a rate-limiting strategy subsequently develop either supraventricular tachycardia or atrial fibrillation. Unlike β-blockers and nondihydropyridine rate-limiting calcium channel blockers, ivabradine provides no protective action at the level of the atrioventricular node and thus patients may be at risk of uncontrolled ventricular rates. The clinical implications of this are uncertain, but it is reassuring that ivabradine can be safely prescribed with β-blockers [Swedberg *et al.* 2010a; Fox *et al.* 2008a].

Future uses

Heart failure

The benefits of heart rate control in heart failure and in particular left ventricular systolic dysfunction are well understood and are multifaceted. When the heart rate is uncontrolled during left ventricular systolic impairment, increased strain is placed on the myocardium to meet physiological oxygen demand. This places the heart at risk of collagen accumulation and eventually left ventricular cardiac remodelling. In turn, this has a prohibitive effect on the heart by reducing the ejection fraction and the stroke volume as well as increasing the end diastolic volume, resulting in decreased functionality (see Figure 3). Other bradycardic agents, principally β-blockers, have a cardioprotective role in stable left ventricular systolic dysfunction. The following studies investigated the potential role and safety of ivabradine in treating heart failure.

In a study in rats with congestive heart failure the use of ivabradine to produce a long-term heart rate reduction was shown to improve the left ventricular function, increase the stroke volume and maintain cardiac output during rate reduction [Mulder *et al.* 2007]. In a small study in humans, a single intravenous dose of ivabradine was administered to patients with regional or global left ventricular systolic impairment [Manz *et al.* 2002]. Heart rate at rest was reduced in the ivabradine group, however cardiac function including stroke volume and ejection fraction were preserved. Ivabradine has also been trialled in patients with NYHA classification III and ejection fractions of $21 \pm 7\%$. Two infusions were found to decrease heart rate, increase stroke volume and left ventricular systolic work without increasing cardiac index [De Ferrari *et al.* 2008].

In heart failure, it is hypothesised that medication which decreases the heart rate will increase diastolic filling time and therefore stroke volume [DiFrancesco and Camm, 2004]. At the same time, myocardial oxygen demand is decreased and myocardial perfusion is increased as a result of the increased duration of diastole. However, the potential benefits may go beyond heart rate reduction. The physiological upregulation of I_f channels in the His–Purkinje system during advanced heart failure requires further

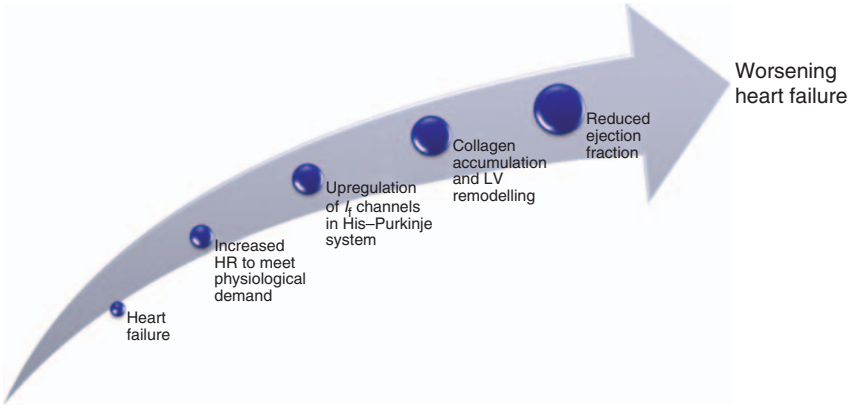

Figure 3. Effect of raised heart rate in heart failure. HR, heart rate; LV, left ventricular.

elucidation and investigation for a potential future target [Savelieva and Camm, 2006]. There is also a need to further study the ability of ivabradine to influence the outcomes of patients with heart failure [Borer, 2006].

The use of ivabradine is currently contraindicated in patients with NYHA classification III–IV and should be used with caution in patients with NYHA classification I–II. No doubt, the results of the BEAUTIFUL and SHIFT studies will result in a review of these cautions.

Acute coronary syndrome

It is proposed that the rate-limiting effects of ivabradine may also be of benefit to patients with acute coronary syndrome (ACS). There are a number of reasons for this. First, ivabradine decreases heart rate, which increases diastole and improves myocardial perfusion while decreasing myocardial oxygen demand. Second, it has been hypothesised that haemodynamic shear forces experienced during systole as a result of contortion of the cardiac arteries may contribute to rupture of atherosclerotic plaques and lesions [Heidland and Strauer, 2001]. It is also known that increased heart rate in patients after a MI increases atherosclerosis [Perski *et al.* 1998]. By decreasing the heart rate without compromising inotropic functionality, ivabradine may provide benefit in these patients while, importantly, maintaining cardiac function. Third, it is theorized that to aid coronary artery perfusion in stenotic arteries, blood flow is rerouted to less stenosed coronary arteries, improving blood flow by using 'subsidiary' vessels [Ferrari *et al.* 2006]. This steal phenomenon has a decreased effectiveness under tachycardic conditions, decreasing perfusion. Finally, the use of β-blockers in patients with ACS can increase the risk of atrioventricular blockade [Shattock and Camm, 2006]. Because ivabradine does not affect conduction via the atrioventricular node, the potential for atrioventricular block would be nullified.

Sinus tachycardia

Inappropriate sinus tachycardia is normally treated with β-blockers, although, β-blockade is not always effective or tolerated. However, there is published evidence, albeit from only one case report, of the effectiveness of ivabradine in the treatment of inappropriate sinus tachycardia [Schulze *et al.* 2008].

Conclusion

The emergence of ivabradine for rate control offers a new treatment option for patients with coronary artery disease and heart failure. A subgroup analysis has shown that ivabradine improves mortality in patients with an initial heart rate greater than 70 bpm and because it can limit heart rate at rest and during exercise, it is particularly useful for treating ambulatory angina pectoris. The main benefit of this bradycardic agent over existing therapies is its more favourable side-effect profile. The lack of negative inotropic action, vasodilation, hypotension and bronchospasm weigh heavily in the favour of ivabradine over β-blockers or rate-limiting calcium channel blockers. Ivabradine should currently be used as a second-line agent for managing angina, or as first-line treatment if the patient is intolerant to β-blockers or there are contraindications. The role of ivabradine in heart failure is still unclear, as well as unlicensed.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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