REVIEW ARTICLE

Drug Safety 2008; 31 (2): 95-107
0114-5916/08/0002-0095/$48.00/0

I_f Inhibition with Ivabradine

Electrophysiological Effects and Safety

Irina Savelieva and *A. John Camm*

Division of Cardiac & Vascular Sciences, St George's University of London, London, UK

Contents

Abstract

Ivabradine belongs to a new class of specific heart rate reducing agents that inhibit spontaneous pacemaker activity of the sinus node by selectively and specifically inhibiting the I_f current; thus, allowing heart rate reduction without affecting myocardial contractility, relaxation and peripheral vascular resistance.

In clinical studies involving >3500 patients and 800 healthy volunteers, ivabradine demonstrated a good safety profile during its clinical development. The most common adverse events were visual symptoms in 16.4% (n = 270) and sinus bradycardia ≤55 beats per minute in 3.2% (n = 53) of all patients treated with recommended doses of 5 mg and 7.5 mg twice daily. However, because the heart rate reducing effect of ivabradine is proportional to the resting heart rate and is associated with a clear trend to a plateau-dose effect, severe sinus bradycardia is uncommon. Less than 1% of patients withdrew from therapy because of untoward sinus bradycardia. The QT interval is prolonged in accordance with the reduction in heart rate; however, after appropriate correction for heart rate and in direct comparisons of the QT interval when the influence of the heart rate was controlled

by atrial pacing, no significant effect of ivabradine on ventricular repolarization duration was demonstrated. Consequently, ivabradine has no direct torsadogenic potential. Because ivabradine also inhibits h-channels, which carry the I_h current in the eye, it may cause luminous phenomena (phosphenes). Visual symptoms are transient, do not interfere with quality of life and have led to few withdrawals (<1%; 24 of 2545 patients); symptoms resolved during treatment in 77.5% (383 of 491) of patients. Since constitutionally active I_f and I_h currents are confined to the sinus node, retina and CNS neurons (ivabradine does not cross blood-brain barrier), ivabradine does not affect other tissues. The safety of ivabradine will be further assessed by postmarketing surveillance and during on-going clinical trials.

A relatively novel group of drugs that reduce heart rate by selectively inhibiting spontaneous pacemaker activity of the sinus node, without compromising myocardial contractility, cardiovascular haemodynamic status or other electrophysiological properties of the heart (the so-called specific and selective sinus node I_f inhibitors), are likely to play a significant role in the management of a wide range of cardiovascular disorders, including coronary artery disease, congestive heart failure and atrial tachyarrhythmias.[1] Among this pharmaceutical entity, ivabradine is the most advanced drug and it is currently approved for clinical use in Europe. Ivabradine has been extensively studied in patients with coronary artery disease and has proven effective in the prevention of angina.[2]

In this article, we explore the effects of I_f current inhibition on cardiac electrophysiology and function, and discuss potential safety considerations of therapy with ivabradine. This review is based on the results of a formal retrospective safety analysis[3] involving >3500 patients and 800 healthy volunteers in 36 countries from Europe, North and South America, Africa, Asia and Australia. The mean age of patients was 60 years. Approximately 34% of the patients were ≥65 years; 17% were women; and about 94% were Caucasian. All patients had a history of coronary artery disease and 53% had previous myocardial infarction.[3]

The review is supplemented by the results of a literature search. The parameters for the literature search were as follows. Original articles published between 1960 and September 2007, focusing on I_f current inhibitors and specifically ivabradine, were identified in MEDLINE and PubMed. The search terms used were 'ivabradine', 'I_f current', 'I_f current inhibitors', 'specific bradycardic agents', 'heart rate', and 'HCN channels'. All papers selected were English-language, full-text papers. We also searched the reference lists of identified articles for further relevant papers. Published abstracts from international scientific conferences were identified, using the same search terms, in journal abstract supplements, abstract CD-ROMs and professional society websites within the last 5 years.

1. I_f Inhibition and Sinus Bradycardia

Ivabradine selectively inhibits the I_f current in the sinus node by binding to the hyperpolarization-activated, cyclic nucleotide-gated (HCN) channels from the intracellular side of the membrane of pacemaker cells.[4] Inhibition of the I_f current is associated with prolongation of spontaneous slow diastolic depolarization of the sinus node, which leads to slowing of heart rate, the primary mechanism of action for the antianginal effect of ivabradine. Ivabradine and its main active metabolite, S 18982, have high affinity to the HCN4 isoform of HCN channels, which is the main isoform in the heart. The concentration of ivabradine that produces 50% inhibition (IC_{50}) of the I_f current carried by HCN4 channels is in the range 1.5–3 μmol/L.[5,6]

1.1 Incidence of Bradycardia

A reduction in heart rate is an expected pharmacological effect of ivabradine. I_f inhibition and the resulting slowing of the sinus node discharge rate is

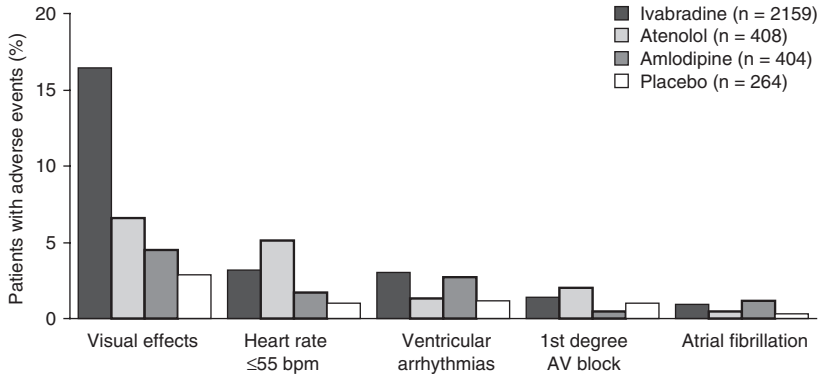

Fig. 1. Visual and cardiac adverse events associated with therapy with ivabradine.[3] **AV** = atrioventricular; **bpm** = beats per minute.

proportional to the resting heart rate.[3] In the safety and efficacy studies, a heart rate of ≤55 beats per minute was reported in 3.2% (53 of 1651) of patients receiving therapeutic doses of ivabradine (i.e. 5 mg or 7.5 mg twice daily), compared with 1.0% (3 of 313) receiving placebo and 1.7% (7 of 404) and 5.1% (21 of 408) of patients treated with active comparators amlodipine and atenolol, respectively (figure 1).[3] The incidence of sinus bradycardia <40 beats per minute was 0.5% with ivabradine 7.5 mg twice daily and 1.7% with atenolol 100 mg daily; no such cases were reported with ivbardine 5 mg twice daily. The proportion of patients with heart rate <40 beats per minute was 0.3% in the whole population, with the recommended doses.[3]

Only 0.2% of patients experienced clinically significant symptomatic bradycardia compared with 0.4% in the atenolol group, and <1% of patients withdrew from therapy (ivabradine only) because of untoward bradycardia.[3] In patients with slow heart rates (<45 beats per minute) on treatment, bradycardia-related symptoms such as hypotension and dizziness were not different in patients treated with ivabradine and patients treated with atenolol, whereas syncope occurred only in the atenolol arm (table I). Dyspnoea and fatigue occurred more commonly with atenolol.[3]

1.2 Heart Rate Dependency of the Rate Lowering Effect

The I_f current is a key current defining the rate of spontaneous slow diastolic depolarization of the sinus node. Nevertheless, computer simulation models have demonstrated that complete blockade of the I_f current would result in a maximum of 30–40% reduction in the sinus node discharge rate.[7,8] In experiments and clinical studies, ivabradine exhibited a plateau dose-response and use-dependent effect on heart rate.[4,9] This is because the pacemaker potential is modulated by several (at least ten) ion channel mechanisms, which are not affected by the drug.[7] Binding of ivabradine to HCN channels is

Table I. Bradycardia-related symptoms in patients with slow heart rate treated with atenolol and ivabradine[3]

Bradycardia-related symptoms[a]	Atenolol	Ivabradine	Ivabradine extension
Number of patients	32	164	67
Number of patient-years	17	71	122
Mean lowest heart rate ± SD (bpm)	41.3 ± 2.4	42.0 ± 2.0	42.3 ± 1.4
Heart rate range (bpm)	35–44	35–44	39–44
Hypotension (%)	0.0	2.8	0.0
Dizziness (%)	6.5	5.7	0.8
Syncope (%)	6.6	0.0	1.6
Fatigue (%)	19.4	2.8	0.0
Dyspnoea (%)	19.4	1.4	0.8

a Rates per 100 patient-years of exposure; bradycardia is defined as a heart rate of <45 bpm.

bpm = beats per minute.

restricted to open channel state and the drug-channel interaction is controlled by the balance between open and close state.[5]

Retrospective analysis in >1300 patients, who received various doses of ivabradine, has shown that the magnitude of the heart rate lowering effect of ivabradine after 3–4 months of treatment appears to be the highest in patients with sinus tachycardia at baseline and the least in those with the lowest baseline heart rate.[10] This is consistent with the known effect of HCN channel function modulation by the autonomic nervous system and accounts for a relatively low incidence of profound bradycardia.

1.3 Cautions to Avoid Bradycardia

Treatment with ivabradine should not be initiated when baseline resting heart rate of the patient is <60 beats per minute to minimize the risk of inappropriately low heart rates during therapy. The dose of ivabradine should be reduced if the heart rate slows to <50 beats per minute or when a symptomatic sinus bradycardia occurs. As ivabradine is metabolized through cytochrome P450 enzyme (CYP) 3A4, the concomitant use of potent CYP3A4 enzyme inhibitors, such as azole antifungals (ketoconazole and itraconazole), antireretroviral drugs and macrolide antibacterials (clarithromycin, erythromicin, josamycin and telethromycin) is strictly contraindicated because these agents may increase plasma concentration and potentiate the heart rate-lowering effect of ivabradine. The association of ivabradine with moderate CYP3A4 inhibitors such as non-dihydropyridine calcium channel antagonists (diltiazem and verapamil) is not recommended. Ivabradine does not inhibit the CYP3A4 enzyme system and co-administration of agents that depend on CYP3A4 metabolism does not increase plasma concentrations of these compounds (figure 2).[3]

2. Effects on Heart Rate Variability

The effects of ivabradine on heart rate variability were studied in the subset of 370 patients who underwent 24-hour Holter ECG recordings at baseline and after 3 months of therapy as part of a larger, prospective, randomized, double-blind, multicentre trial that included 1195 patients with coronary artery disease and stable angina.[11] Therapy with ivabradine was associated with a significant im-

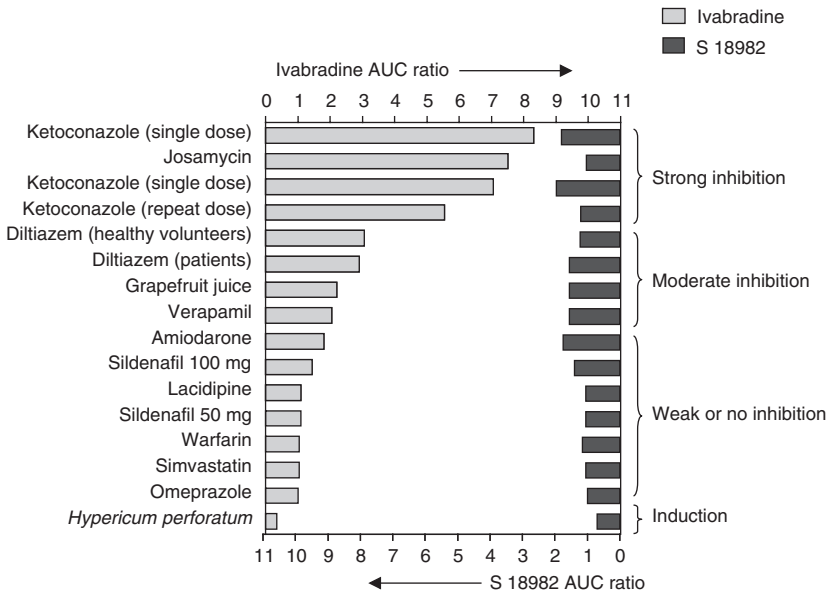

Fig. 2. Ratios of area under the plasma concentration-time curve (AUC) of ivabradine or its metabolite S 18982 in the presence of cytochrome P450 enzyme 3A4 inhibitors, substrates or inducers.[3]

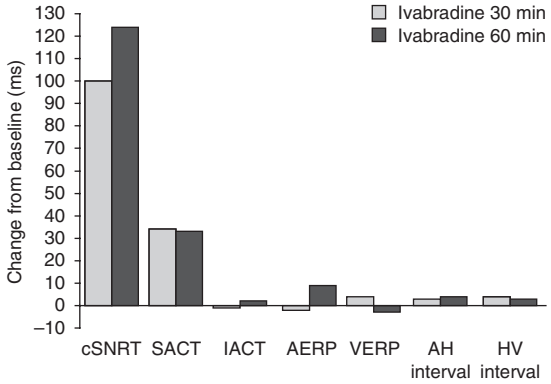

Fig. 3. Electrophysiological effects of a single intravenous bolus of ivabradine 2 mg/kg in electrophysiological studies at 30 minutes and 1 hour after infusion.[14] **AERP** = atrial effective refractory period; **cSNRT** = corrected sinus node recovery time; **IACT** = intra-atrial conduction time; **SACT** = sinoatrial conduction time; **VERP** = ventricular effective refractory period.

provement in both time-domain and frequency-domain parameters of heart rate variability, particularly those reflecting parasympathetic activity, compared with amlodipine.[12]

Sympathovagal balance measured by the ratio of low-to-high frequency powers improved with both drugs, but this improvement was statistically significant only for ivabradine.[12] The observation that high frequency power increased after 3 months of therapy with ivabradine and did not change on amlodipine, in spite of similar anti-anginal and anti-ischaemic effects, suggests that ivabradine may act to increase parasympathetic tone. It is unclear whether this increase is purely the result of heart rate lowering action of ivabradine or is an additional benefit of I_f inhibition.

3. Effects of Ivabradine on Cardiac Electrophysiology

3.1 Acute Electrophysiological Studies

The effects of a single intravenous bolus of ivabradine (0.2 mg/kg over 15 seconds) were assessed in 36 patients with normal or near-normal baseline electrophysiological parameters during electrophysiological studies.[13] Ivabradine significantly reduced heart rate, but produced little or no effect on the atrioventricular node, His-Purkinje system, and atrial and ventricular refractoriness (figure 3).[14] Ivabradine was associated with an increase in corrected sinus node recovery time by 90–120 ms at 30 minutes and 1 hour after drug administration.[14] This effect is a consequence of a slower rate of depolarization in the sinoatrial region resulting from inhibition of the I_f current.

A non-significant trend towards an increase in sinoatrial conduction time was observed with ivabradine.[14] This interval includes time for conduction of the paced atrial beat through the perinodal tissue into the sinus node, resetting of the sinus node and conduction of the spontaneous impulse that follows through the perinodal tissue into the atrium. In the presence of ivabradine, the I_f current, an important contributor to cell spontaneous diastolic depolarization in the sinus node, is reduced; therefore, the time taken for pacemaker cells to reach the depolarization threshold to initiate the action potential and activate the adjacent cells is increased. Consequently, conduction time through the sinus node and adjacent myocardium is delayed.

There is experimental evidence suggesting that inhibition of the I_f current and the subsequent reduction of heart rate by ivabradine may stimulate ionic remodelling in sinoatrial cells in mice, including upregulation of (i) genes encoding HCN2 and HCN4 channels, which carry the I_f current; (ii) Kir2.1 channels, which regulate the inward rectifier potassium current; and (iii) type 2 ryanodine Ryr2 channels.[15] In addition, ivabradine downregulates the Cav3.1 channel responsible for T-type inward calcium current ($I_{Ca,T}$).[15] Ivabradine increased the expression of HCN2 and HCN4 genes by 24% and 52%, respectively.[15] These effects were confined to sinoatrial cells and were not observed in the ventricles. The physiological significance of these findings has yet to be explored. Upregulation of HCN channels may occur as an adaptation mechanism in response to inhibition of the I_f current by ivabradine. It may have a potential clinical implication in the loss of efficacy of I_f inhibitors or to a significant increase in heart rate after discontinuation of the drug. However, clinical studies showed no rebound

Table II. Percentage of inhibition of sinus node ion currents by ivabradine in rabbit sinoatrial cells using the patch-clamp technique (reproduced from DiFrancesco and Camm,[1] with permission)

Ion current	Concentration of ivabradine (μmol/L) [mean ± SE]				
	0.03	0.3	1	3	10
I_f	5.5 ± 1.0	19.5 ± 2.2	32 ± 3	59 ± 2	80 ± 2
$I_{Ca,T}$	0	0	0	0	0
$I_{Ca,L}$	0	0	0	0	18 ± 1
I_K	0	0	0	0	16 ± 1

$I_{Ca,L}$ = long-lasting calcium current; $I_{Ca,T}$ = transient calcium current; I_f = current carried by hyperpolarization-activated, cyclic nucleotide-gated cation channels; I_K = potassium current.

effect after abrupt termination of treatment with high doses of ivabradine.[16]

Acute intravenous studies[13,14] and the NESI (Non-invasive Electrophysiological Study of Ivabradine) trial, in 27 patients fitted with the telemetric programmed stimulation facility in whom ivabradine was administered orally for 3.5 days,[17] demonstrated no clinically significant effect of the drug on the ventricular effective refractory period.

Consistent with these observations, in the overall patient population exposed to ivabradine,[3] the incidence of heart block, QRS widening or bundle branch block was low and comparable with placebo and was likely to reflect naturally occurring events in a large patient population with coronary artery disease and previous myocardial infarction.

3.2 I_f Inhibition and Ventricular Repolarization

At the mean total plasma concentration (C_{max}) of approximately 0.1 μmol/L associated with a dose of 10 mg twice daily, i.e. at a dose higher than that recommended in humans, ivabradine is highly selective for the I_f current, with no effect on L- and T-type calcium currents and the delayed rectifier potassium current I_K (table II).[6] *In vitro*, ivabradine inhibits the human ether-a-go-go related gene (hERG) potassium channel that carries the rapid delayed rectifier current (I_{Kr}), with an IC_{50} of 4.9 μmol/L, which is approximately 70-fold higher than mean total plasma concentration C_{max} in patients treated with 7.5 mg of ivabradine twice daily and 240-fold higher when considering the unbound plasma fraction (approximately 30%), which is well above the commonly accepted 30-fold safety margin.[1] In guinea pig papillary muscles, no prolongation of action potential duration was observed at concentrations up to 10 μmol/L[18] (figure 4). In conscious dogs, long-term (up to 1 year) exposure to oral ivabradine at doses sufficient to produce C_{max} values 134-fold and 100-fold the C_{max} achieved by a human regimen of 7.5 mg and 10 mg twice daily, respectively, did not affect the QTc interval.[3]

In clinical studies of ivabradine, the uncorrected QT interval was prolonged by 18–30 ms in accordance with the reduction in heart rate and in a dose-dependent fashion.[11,16] The incidence of drug-induced QT interval prolongation ≥500 ms or ≥60 ms from baseline, was reported in the range of 0.2–1.6% for ivabradine 5–10 mg twice daily compared with 0% for atenolol 100 mg once daily (table III). After appropriate correction for heart rate using a population-specific rate correction formula,[19] an increase in the QT interval with ivabradine did not exceed 2 ms, which was below the limit of 5 ms for torsadogenicity established by the consensus of the International Conference on Harmonisation on the Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.[20]

In the NESI study of 27 patients with permanent pacemakers, direct comparisons of the uncorrected QT interval when heart rate was controlled by atrial pacing at a series of identical rates showed that ivabradine 5 mg or 10 mg twice daily had no direct effect on ventricular repolarization duration.[17] Therefore, the torsadogenic potential of ivabradine

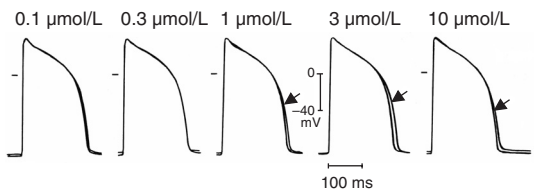

Fig. 4. Ivabradine at doses 0.1–10 μmol/L did not prolong action potential duration in guinea pig papillary muscles after a 30-minute exposure. Representative recordings of action potentials showing maximal effects of ivabradine (arrows) superimposed on respective action potential recordings at baseline. The preparations were driven at 1 Hz (reprinted by permission from Macmillan Publishers Ltd: Br J Pharmacol. Thollon et al.,[18] 1994©).

Table III. Incidence of QT interval prolongation of potential concern during treatment with ivabradine and atenolol[19]

QT Interval	Ivabradine				Atenolol	Amlodipine
	5 mg bd [n (%)]	7.5 mg bd [n (%)]	10 mg bd [n (%)]	all [n (%)]	100 mg od [n (%)]	10 mg od [n (%)]
QT (uncorrected)						
No. of patients	170	448	530	1148	91	299
QT ≥500 ms	2 (1.2)	7 (1.6)	3 (0.6)	12 (1.0)	0	0
QT ≥500 ms and change ≥60 ms	0	3 (0.7)	1 (0.2)	4 (0.3)	0	0
QTcP (population corrected)						
No. of patients	169	447	524	1140	91	298
QTcP ≥500 ms	0	1 (0.2)	0	1 (0.1)	1 (1.1)	0
QTcP ≥500 ms and change ≥60 ms	0	0	0	0	0	0

bd = twice daily; **od** = once daily.

appears to be low and other than for QT prolongation directly consequent on bradycardia, ivabradine does not appear to have any direct proarrhythmic effect.

However, the potential importance of a prolonged uncorrected QT value is not clear and may give rise to arrhythmia in patients at high risk of drug-induced torsades de pointes, e.g. patients with congenital long QT syndrome or individuals with acquired long QT syndrome due to other QT-prolonging drugs.

4. Cardiac Arrhythmias

4.1 Ventricular Arrhythmias

Bradycardia *per se* is a risk factor for ventricular tachyarrhythmias, particularly torsade de pointes, because of QT lengthening due to the reverse use-dependency of several ion channels that are responsible for ventricular repolarization. Treatment with ivabradine, even when significant bradycardia occurred, was not associated with an excess of ventricular proarrhythmias.[3] The incidence of ventricular premature beats recorded on the 12-lead ECG and during 24-hour ambulatory Holter monitoring or noted during an exercise stress test did not differ in patients receiving ivabradine, amlodipine, atenolol or placebo (2.8%, 2.7%, 1.2% and 1.3%, respectively).[3] There were 11 documented cases of ventricular tachycardia (sustained and non-sustained) in nearly 3000 patients treated with ivabradine; the overall incidence of ventricular tachycardia that occurred in association with ivabradine and atenolol was 0.38% and 0.2%, respectively. Patients with risk factors for drug-induced ventricular proarrhythmias, that is female gender, elderly age, left ventricular hypertrophy, congestive heart failure and hypokalaemia, did not appear to experience more ventricular arrhythmias with ivabradine than with amlodipine or atenolol.

4.2 I_f Current and Arrhythmias in Failing Hearts

HCN channels are present in the His-Purkinje system and ventricular myocardium, but the I_f cur-

rent activates at more negative potentials in Purkinje cells and ventricles than in the sinus node (approximately −85 mV and −120 mV vs −50 mV, respectively).[5] Because the I_f current contributes to the spontaneous diastolic depolarization phase in Purkinje cells, I_f inhibition may theoretically suppress subsidiary pacemaker activity. However, ivabradine is more selective to the HCN4 isoform than the HCN2 isoform,[7] which is specific for the sinus node, whereas the expression of the HCN4 is low in Purkinje fibres and ventricles. Conversely, in failing hearts, the density of HCN channels and the I_f current are increased as part of complex ionic remodelling, which may have important potential implications regarding ventricular arrhythmogenesis, particularly related to enhanced automaticity.[21-23] Changes in autonomic regulation with a shift towards a higher sympathetic tone associated with end-stage heart failure may also influence the I_f current expression in ventricular myocardium. Consequently, inhibition of the I_f current in these circumstances may have an antiarrhythmic effect or might suppress idioventricular rhythms.

4.3 Effects on the Atrial Myocardium

There is evidence that the I_f current may play a role in causing abnormal diastolic depolarization of atrial myocardium and contributes to ectopic atrial automaticity, particularly during β-adrenoceptor or serotonin stimulations.[24,25] Recent experiments in a canine congestive heart model have demonstrated differences in the expression of HCN subunits in the normal and remodelled sinoatrial node and right atrium.[26] Heart failure is associated with down-regulation of the HCN4 subunit in the sinus node, which may contribute to sinus node dysfunction. Conversely, the amount of the HCN4 subunit was increased in the right atrium, which may predispose to ectopic impulse formation. The expression of messenger RNA (mRNA) of the HCN channels in the free wall of human atria and atrial appendages is upregulated in the presence of atrial fibrillation and the increased left atrial filling pressure.[27] The existence of the I_f current was demonstrated in human atrial myocytes isolated from dilated atria, which exhibited spontaneous diastolic depolarization.[25,28] Pharmacological interventions, such as stimulation of adenosine and muscarinic receptors and administration of class IC antiarrhythmic agent propafenone, inhibited activity of the I_f current.[29] Ivabradine has recently been shown to inhibit the I_f current in isolated human atrial myocytes.[30] However, activation of the I_f current in atrial myocytes was observed at more negative potentials than in pacemaker cells within the sinus node and its contribution to arrhythmogenesis has yet to be investigated.[28]

Ivabradine has been shown to produce a concentration-dependent block of human cloned hKv1.5 channels, which are responsible for the ultrarapid delayed rectifier current (I_{Kur}) recorded in human atrial myocytes.[31] This block was also voltage-dependent and increased steeply between −30 mV and 0 mV, which corresponded to the voltage range for I_{Kur} channel opening. It is an interesting finding since blockade of the I_{Kur} current, which is restricted to the atrial myocardium, is a novel concept of antiarrhythmic drug therapy for atrial fibrillation.

In clinical electrophysiological studies, ivabradine did not affect intra-atrial conduction time or atrial refractoriness.[13,14] In efficacy and safety studies, the incidence of atrial fibrillation was similar with amlodipine, atenolol and ivabradine (1.2%, 0.9% and 1%, respectively).[3] Ivabradine has no blocking effect on the atrioventricular node and is ineffective at reducing heart rate in patients with permanent atrial fibrillation. Because the functional status of HCN channels in fibrillating atria and the effects of I_f current inhibitors are yet to be further explored, ivabradine should probably be avoided in such patients as well as in patients with frequent episodes of paroxysmal atrial fibrillation.

5. I_f Inhibition and Left Ventricular Function

Experimental studies using a chronic heart failure model in rats have demonstrated that ivabradine effectively reduced heart rate, increased stroke volume, decreased left ventricular systolic diameter and improved myocardial function, probably due to its

ability to shift the ventricular systolic pressure-volume curve leftwards and reduce collagen accumulation.[32,33] Ivabradine does not affect vascular relaxation and has been shown to produce an antihypertrophic effect on the aorta in rats with spontaneous hypertension.[34] In a canine model of exercise-induced myocardial stunning, pre-treatment with ivabradine consistently accelerated the recovery of stunned myocardium by 50% compared with atenolol.[35] This trend was distinguished more clearly when agents were administered after the induction of stunning.

In the clinical setting, ivabradine did not affect global myocardial contractility or increase the incidence of new onset heart failure in patients with preserved left ventricular systolic function (0.3% vs 0.5% with atenolol or amlodipine); however, there is insufficient clinical experience in patients with ventricular dysfunction.[36] Intravenous administration of ivabradine 0.25 mg/kg in the heterogeneous patient population with regional and global left ventricular dysfunction had no effect on left ventricular ejection fraction, fractional shortening and stroke volume.[36] Conversely, in patients with severely depressed systolic function (mean ejection fraction 20%) and class III New York Heart Association (NYHA) heart failure, the reduction in heart rate following intravenous administration of ivabradine was associated with a significant increase in stroke volume and left ventricular work by a maximum of 50% and 48%, respectively, at 4 hours.[37] There was also a trend towards an increase in cardiac index. These findings have been reproduced in a double-blind, placebo-controlled trial of 65 patients with coronary artery disease, NYHA class II and a mean left ventricular ejection fraction of 40%, which has shown that therapy with ivabradine resulted in the reduction in left ventricular volumes at 3 months compared with placebo (figure 5).[38] The effect was more apparent in patients with significantly impaired systolic function and those with an ejection fraction <35%.

5.1 Large Randomized Studies

However, the consistency of this effect in the long term is unknown. Two large-scale randomized studies in patients with left ventricular dysfunction are under way. The BEAUTIFUL (morBidity-mortality EvAlUaTion of the I_F inhibitor ivabradine in patients with coronary artery disease and left ventricULar dysfunction) trial is designed to investigate whether ivabradine may prevent death and major cardiovascular events in >10 000 patients with ejection fraction of <40% and left ventricular dilation (short axis diameter >56 mm).[39] Patients have been randomized to ivabradine, starting at 5 mg twice daily and up-titrated to 7.5 mg twice daily if resting heart rate does not fall below 60 beats per minute, or placebo. The study has 90% power to detect a 19% relative reduction in the risk of the primary composite endpoint of cardiovascular death, hospitalization for acute myocardial infarction and hospitalization

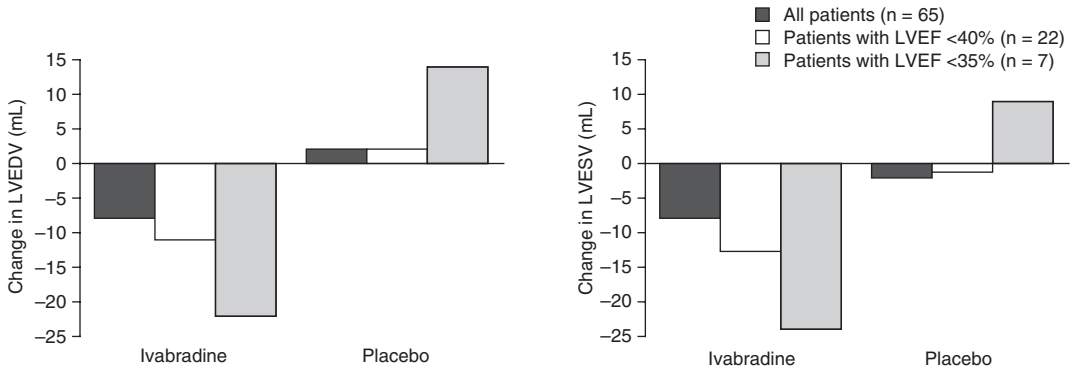

Fig. 5. Effects of ivabradine on left ventricular end diastolic volume (LVEDV) and left ventricular end systolic volumes (LVESV) in patients with coronary artery disease and left ventricular ejection fraction (LVEF) >30% and <45%.[38]

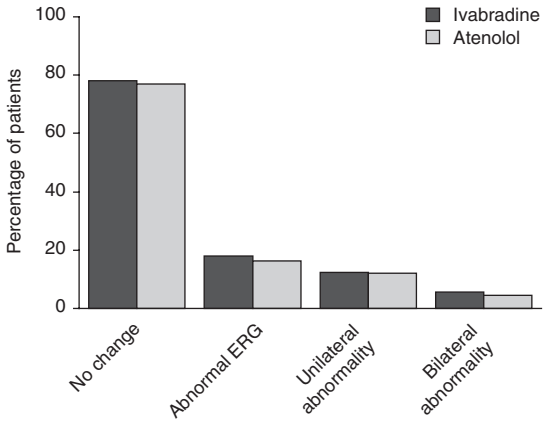

Fig. 6. Comparison of the effects of ivabradine and atenolol on the electroretinograms (ERG) in 426 patients.[3]

for new onset or worsening heart failure, assuming an event incidence of 11% at 2.25 years in the placebo group and an incidence of non-cardiovascular death of 1% in both groups. The recruitment has been completed and the results are expected in September 2008 after the completion of 1-year follow-up of the last recruited patient.

The SHIFT (Systolic Heart failure treatment with IF inhibitor ivabradine Trial) study will randomize approximately 5500 patients with overt moderate to severe heart failure and ejection fraction <35% (about two-thirds will be patients with ischaemic cardiomyopathy).

6. Inhibition of Hyperpolarization-Activated, Cyclic Nucleotide-Gated (HCN) Channels in Other Organs

6.1 Inhibition of HCN Channels in the Eye

HCN channels, formed predominantly by HCN1 and HCN2 isoforms, are also responsible for the I_h current in the retina that is involved in the response to light stimuli. In experiments, inhibition of the I_h current caused dose-dependent changes of the electroretinogram, mainly in the cone system responses of the retina.[40,41] Extensive testing showed that ivabradine was not associated with any alteration of ocular structures or permanent visual disturbances.[3]

The effect of ivabradine on retinal function was assessed by electroretinography in a subset of 426 patients, many of whom also had a concomitant condition that carried a risk of ophthalmic complications, including hypertension (60%), diabetes mellitus (16%) and/or a history of ophthalmic disease (20–30%), mainly cataract, dyschromatopsia and glaucoma.[3] Ivabradine caused a bilateral decrease in b-wave amplitude in a similar proportion of patients to atenolol, whereas bilateral reversible increase in latency was seen with ivabradine (5.4%); these changes are mild and reversible and are not likely to be of potential clinical concern (figure 6). Furthermore, none of the patients showed retinal degeneration or other permanent alteration of retinal function or morphology that could not be explained by an underlying condition. Long-term follow-up does not give rise to any concern either. In the majority of patients, the ophthalmic changes improved or resolved at subsequent investigations.

I_h channel blockade by ivabradine result in luminous phenomena (phosphenes) in approximately 15% of patients receiving therapeutic doses of ivabradine (figure 7).[3] These effects are often triggered by changes in luminosity from dark to light. Generally, visual symptoms associated with ivabradine are transient, do not interfere with quality of life and have led to few withdrawals (<1%) with complete recovery after discontinuation of the drug. Visual acuity, colour vision and visual fields were unaffected and visual symptoms do not affect driving. Ivabradine inhibition of the I_h current did not affect driving performance assessed using a driving simulator in 75 subjects exposed to high doses of ivabradine (10–15 mg twice daily) compared with 15 subjects exposed to placebo.[3]

6.2 Inhibition of HCN Channels in the CNS

HCN channels are present in numerous cell types in the CNS, including neurons in the hippocampus, amygdala, thalamus and hypothalamus, substantia nigra, inferior olive, dorsal raphe and cerebellum.[42] In cortical pyramidal neurons, presynaptic terminals

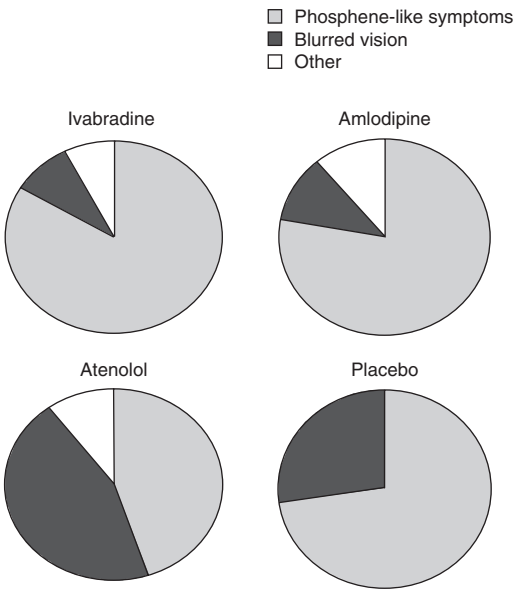

Fig. 7. Type and distribution of visual symptoms reported as adverse events.[3]

of cerebellar basket cells and basal ganglia, the I_h current contributes greatly to intrinsic cellular properties and synchronized neuronal activity. Substantial inhibition of the I_h current in the CNS and associated symptoms were one of the reasons for the withdrawal of some first-generation specific bradycardia agents, such as alinidine, falipamil and ZD-7288, from further development.[43] In contrast, ivabradine does not cross the blood-brain barrier and therefore does not cause central nervous symptoms.[13]

7. I_f Inhibition and Prognosis

All-cause mortality rates per 100 patient-years were similar in the ivabradine, placebo and amlodipine groups, and lowest in the atenolol group (table IV).[3] Two patients who died in the ivabradine group were also receiving amlodipine, as were both patients who died in the placebo group. Most deaths were cardiovascular related and 16 were sudden. Overall, all-cause mortality with ivabradine did not differ from predicted for patient populations with stable coronary artery disease (2–3% per year). Although atenolol was associated with lower all-cause mortality, this trend was not statistically significant. In addition, the design of the studies might lead to bias in terms of comparison of the safety of ivabradine and atenolol, because about two-thirds of the patients had previously received β-adrenoceptor antagonists (β-blockers) and were known to tolerate these drugs, and patients with known intolerance or contraindications to atenolol were specifically excluded.

8. Conclusions

Ivabradine is the only clinically used selective inhibitor of the I_f current, which has proven to be effective for prevention of angina pectoris in patients with stable coronary artery disease. The general safety of ivabradine with regard to the incidence of adverse events is in line with what was observed in the other treatment groups. No further adverse events (other than visual disturbances and sinus bradycardia) were identified as related to ivabradine, and there was no evidence of excess in mortality with ivabradine. There are several on-going studies, including the large randomized BEAUTIFUL trial of the effects of ivabradine on cardiovascular morbidity and mortality in patients with left ventricular dysfunction and coronary artery disease, and the SHIFT study in patients with overt heart failure.

Table IV. Deaths per patient-years of treatment in the ivabradine, amlodipine, atenolol and placebo groups[3]

Drug	Number of patients	Patient-years	Deaths per 100 patient-years (%)	95% CI
Ivabradine	2907	1107.2	2.44	1.61, 3.55
Atenolol	435	210.9	0.50	0.02, 2.76
Amlodipine	404	95.9	2.09	0.25, 7.54
Placebo	313	65.2	3.07	0.37, 11.09

Acknowledgements

Professor Camm is a chairman of the Data Safety Committee for the BEAUTIFUL (morBidity-mortality EvAlUaTion of the I_F inhibitor ivabradine in patients with coronary artery disease and left ventricULar dysfunction) study and a member of the Ivabradine Data Monitoring Committee, which are both sponsored by Servier. Dr Savelieva is a former investigator for the NESI (Non-invasive Electrophysiological Study of Ivabradine study) trial, which was sponsored by Servier. No sources of funding were used in the preparation of this article.

References

1. DiFrancesco D, Camm JA. Heart rate lowering by specific and selective I_f current inhibition with ivabradine: a new therapeutic perspective in cardiovascular disease. Drugs 2004; 64: 1757-65
2. Tardif JC. Clinical results of I(f) current inhibition by ivabradine. Drugs 2007; 67 Suppl. 2: 35-41
3. European Medicines Agency: Committee for Medicinal Products for Human European Public Assessment Report (EPAR), Procoralan [online]. Available from URL: http://www.emea.eu.int [Accessed 2008 Jan 14]
4. Bucchi A, Baruscotti M, DiFrancesco D. Current-dependent block of rabbit sino-atrial node I_f channels by ivabradine. J Gen Physiol 2002; 120: 1-13
5. Baruscotti M, Bucchi A, Difrancesco D. Physiology and pharmacology of the cardiac pacemaker ("funny") current. Pharmacol Ther 2005; 107: 59-79
6. Bois P, Bescond J, Renaudon B, et al. Mode of action of bradycardic agent, S 16257, on ionic currents of rabbit sinoatrial node cells. Br J Pharmacol 1996; 118: 1051-7
7. Robinson RB, Siegelbaum SA. Hyperpolarization-activated cation currents: from molecules to physiological function. Annu Rev Physiol 2003; 65: 453-80
8. Robinson RB, DiFrancesco D. Sinoatrial node and impulse initiation. In: Spooner PM, Rosen MR, editors. Foundations of cardiac arrhythmias: basic concepts and clinical approaches. New York: Marcel Dekker, 2001: 151-70
9. Thollon C, Bedut S, Villeneuve N, et al. Use-dependent inhibition of hHCN4 by ivabradine and relationship with reduction in pacemaker activity. Br J Pharmacol 2007; 150: 37-46
10. Savelieva I, Borer JS, Camm AJ. Heart rate lowering action of ivabradine depends on baseline heart rate: mechanism of low incidence of excessive bradycardia during therapy with ivabradine [abstract]. Heart 2007; 93 Suppl. 1: A45
11. Ruzyllo W, Tendera M, Ford I, et al. Antianginal efficacy and safety of ivabradine compared with amlodipine in patients with stable effort angina pectoris: a 3-month randomised, double-blind, multicentre, noninferiority trial. Drugs 2007; 67: 393-405
12. Camm AJ, Le Heuzey JY, Jern S, et al. Heart rate variability is significantly increased by ivabradine compared with amlodipine in patients with coronary artery disease: a prospective randomised, double-blind, controlled study [abstract]. J Am Coll Cardiol 2007; 49 Suppl. A: 26A
13. Savelieva I, Camm AJ. Novel I_f current inhibitor ivabradine: safety considerations. In: Camm AJ, Tendera M, editors. Advances in cardiology. Heart rate slowing by pharmacological I_f current inhibition: role in cardiovascular disease. Basel: Karger AG, 2006; 43: 79-96
14. Camm AJ, Lau CP. Electrophysiological effects of a single intravenous administration of ivabradine (S 16257) in adult patients with normal baseline electrophysiology. Drugs RD 2003; 4 (2): 83-9
15. Leoni AL, Marionneau C, Demolombe S, et al. Chronic heart rate reduction remodels ion channel transcripts in the mouse sinoatrial node but not in the ventricle. Physiol Genomics 2005; 24: 4-12
16. Tardif JC, Ford I, Tendera M, et al. INITIATIVE Investigators. Efficacy of ivabradine, a new selective I(f) inhibitor, compared with atenolol in patients with chronic stable angina. Eur Heart J 2005; 26: 2529-36
17. Savelieva I, Jones S, Dougal K, et al. Non-invasive Electrophysiological Study of Ivabradine (NESI) in patients with dual chamber pacemakers: effects on ventricular repolarization [abstract]. J Am Coll Cardiol 2006; 47 Suppl. A: 27A
18. Thollon C, Cambarrat C, Vian J, et al. Electrophysiological effects of S 16257, a novel sino-atrial node modulator, on rabbit and guinea-pig cardiac preparations: comparison with UL-FS 49. Br J Pharmacol 1994; 112: 37-42
19. Savelieva I, Camm AJ. Comparison of the effects of a selective I_f current inhibitor ivabradine and atenolol on the QT interval in patients with coronary artery disease [abstract]. Heart Rhythm 2005; 2: S145-6
20. International Conference on Harmonisation; guidance on E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. Fed Regist 2005; 70: 61134-5
21. Hoppe UC, Jansen E, Sudkamp M, et al. Hyperpolarization-activated inward current in ventricular myocytes from normal and failing human hearts. Circulation 1998; 97: 55-65
22. Cerbai E, Sartiani L, DePaoli P, et al. The properties of the pacemaker current I(f) in human ventricular myocytes are modulated by cardiac disease. J Mol Cell Cardiol 2001; 33: 441-8
23. Han W, Zhang L, Schram G, et al. Properties of potassium currents in Purkinje cells of failing human hearts. Am J Physiol Heart Circ Physiol 2002; 283: H2495-503
24. Michels G, Er F, Khan I, et al. Single-channel properties support a potential contribution of hyperpolarization-activated cyclic nucleotide-gated channels and If to cardiac arrhythmias. Circulation 2005; 111: 399-404
25. Porciatti F, Pelzmann B, Cerbai E, et al. The pacemaker current I(f) in single human atrial myocytes and the effect of beta-adrenoceptor and A1-adenosine receptor stimulation. Br J Pharmacol 1997; 122: 963-9
26. Zicha S, Fernandez-Velasco M, Lonardo G, et al. Sinus node dysfunction and hyperpolarization-activated (HCN) channel subunit remodeling in a canine heart failure model. Cardiovasc Res 2005; 66: 472-81
27. Lai LP, Su MJ, Lin JL, et al. Measurement of funny current (I(f)) channel mRNA in human atrial tissue: correlation with left atrial filling pressure and atrial fibrillation. J Cardiovasc Electrophysiol 1999; 10: 947-53
28. Hoppe UC, Beuckelmann DJ. Characterization of the hyperpolarization-activated inward current in isolated human atrial myocytes. Cardiovasc Res 1998; 38: 788-801
29. Hoppe UC, Beuckelmann DJ. Modulation of the hyperpolarization-activated inward current (If) by antiarrhythmic agents in isolated human atrial myocytes. Naunyn Schmiedebergs Arch Pharmacol 1998; 358: 635-40

30. El Chemaly A, Magaud C, Patri S, et al. The heart rate-lowering agent ivabradine inhibits the pacemaker current If in human atrial myocytes. J Cardiovasc Electrophysiol 2007; 18: 1190-6
31. Delpón E, Valenzuela C, Pérez O, et al. Mechanism of block of a human cloned potassium channel by the enantiomers of a new bradycardic agent: S-16257-2 and S-16260-2. Br J Pharmacol 1996; 117: 1293-301
32. Mulder P, Barbier S, Chagraoui A, et al. Long-term heart rate reduction induced by the selective I(f) current inhibitor ivabradine improves left ventricular function and intrinsic myocardial structure in congestive heart failure. Circulation 2004; 109: 1674-9
33. Simon L, Ghaleb B, Puybasset L, et al. Coronary and hemodynamic effects of S 16257, a new bradycardic agent, in resting and exercising conscious dogs. J Pharmacol Exp Ther 1995; 275: 659-66
34. Albaladejo P, Carusi A, Apartian A, et al. Effect of chronic heart rate reduction with ivabradine on carotid and aortic structure and function in normotensive and hypertensive rats. J Vasc Res 2003; 40: 320-8
35. Monnet X, Colin P, Ghaleb B, et al. Heart rate reduction during exercise-induced myocardial ischaemia and stunning. Eur Heart J 2004; 25: 579-86
36. Manz M, Reuter M, Lauck G, et al. A single intravenous dose of ivabradine, a novel I(f) inhibitor, lowers heart rate but does not depress left ventricular function in patients with left ventricular dysfunction. Cardiology 2003; 100: 149-55
37. De Ferrari GM, Mazzuero A, Agnesina L, et al. Ivabradine infusion in patients with severe heart failure is safe, reduces heart rate and increases left ventricular stroke volume and systolic work [abstract]. Eur Heart J 2006; 27: 330
38. Jondeau G, Korewicki Y, Vasiliauskas D. Effect of ivabradine in patients with left ventricular systolic dysfunction and coronary artery disease [abstract]. Eur Heart J 2004; 25 (Suppl.): 491
39. Fox K, Ferrari R, Tendera M, et al. BEAUTIFUL Steering Committee. Rationale and design of a randomized, double-blind, placebo-controlled trial of ivabradine in patients with stable coronary artery disease and left ventricular systolic dysfunction: the morBidity-mortality EvAlUaTion of the I(f) inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction (BEAUTIFUL) study. Am Heart J 2006; 152: 860-6
40. Demontis GC, Longoni B, Barcaro U, et al. Properties and functional roles of hyperpolarization-gated currents in guinea-pig retinal rods. J Physiol 1999; 515: 813-28
41. Gargini C, Demontis GC, Bisti S, et al. Effects of blocking the hyperpolarization-activated current (Ih) on the cat electroretinogram. Vision Res 1999; 39: 1767-74
42. Monteggia LM, Eisch AJ, Tang MD, et al. Cloning and localization of the hyperpolarization-activated cyclic nucleotide-gated channel family in rat brain. Brain Res Mol Brain Res 2000; 81: 129-39
43. Yusuf S, Camm AJ. Sinus tachyarrhythmias and the specific bradycardic agents: a marriage made in heaven? J Cardiovasc Pharmacol Ther 2003; 8: 89-105

Correspondence: Professor *A. John Camm*, Division of Cardiac & Vascular Sciences, St George's University of London, Cranmer Terrace, London, SW17 0RE, UK.
E-mail: jcamm@sgul.ac.uk