

Sinus Node I_f Channel Inhibition – A New Therapeutic Approach to Heart Rate Lowering

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Abstract: Heart rate lowering has an important role in the treatment of coronary artery disease. Lower heart rates extend diastolic filling, facilitating improved myocardial perfusion and reduced myocardial oxygen demand. This has traditionally been achieved with beta-blockers or calcium-channel blockers. Unfortunately both these classes of drugs have side-effects in a significant minority of patients.

The recent development of ivabradine, which acts specifically on the sinoatrial node, offers promise in achieving heart rate reduction without major side effects. Ivabradine selectively and specifically inhibits the I_f channel which is integral to the generation of the pacemaker current in the sinoatrial node. Initial studies utilising ivabradine show improvements in exercise tolerance and time to developing ischaemia during exercise in patients with chronic stable angina. Ivabradine has no negative inotropic effects and does not appear to have any major side-effects. It has been shown to have similar anti-anginal and anti-ischaemic effects to atenolol and amlodipine. Animal studies have suggested that ivabradine may have beneficial effects in chronic heart failure leading to improvements in left ventricular function. In humans with stable coronary artery disease, left ventricular dysfunction and heart rates of 70bpm or more, ivabradine appears to reduce rates of revascularisation and hospitalisation for myocardial infarction.

Key Words: Funny channel, Ivabradine, chronic stable angina, heart rate lowering.

INTRODUCTION – THE IMPORTANCE OF HEART RATE

Coronary heart disease (CHD) remains one of the most significant health care problems in the world in terms of morbidity and mortality with more than 100,000 deaths per year from CHD in the UK alone [1]. In addition to the acute effects of CHD, there are approximately 2 million people with chronic stable angina in the UK many of whom remain symptomatic despite best current medical therapy [1]. Stable angina affects 3-4 % of the population in Europe and the United States [2]. Angina occurs when myocardial oxygen demand is greater than oxygen delivery, usually due to reduced blood flow secondary to atherosclerotic coronary artery disease. Heart rate reduction decreases myocardial oxygen demand and increases perfusion by increasing diastolic filling time in the coronary circulation (Fig. 1). Heart rate reduction is also important in the treatment of patients with acute coronary syndromes (including myocardial infarction) [3] and heart failure [4,5]. Furthermore, a chronically high heart rate is associated with a poorer outcome in patients with angina [6], hypertension [7], heart failure [8] and also the general population [9]. Higher heart rates are associated with increased atherosclerosis and acute plaque rupture, presumably due to increased turbulence and wall stress (Fig. 2). Thus, in addition to improving symptoms, heart rate reduction is an important component of the treatment of patients at increased risk of death from cardiac disease.

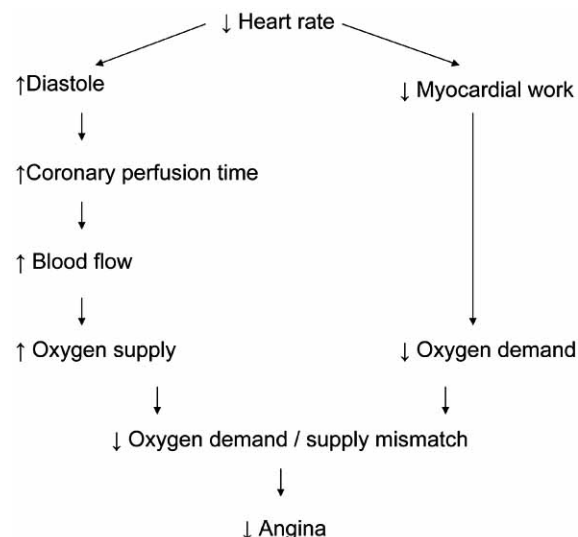


Fig. (1). Anti-ischaemic effects of heart rate lowering.

WHAT DETERMINES HEART RATE? THE SINU-ATRIAL NODE AND PACEMAKER CURRENT

Spontaneous electrical activity can occur in many parts of the heart. However, in patients in sinus rhythm, heart rate is determined by the activity of the sinoatrial (SA) node. Specialized pacemaker cells within the SA node slowly depolarise, due to the flux of ions described in more detail below. This depolarisation raises the membrane potential towards the threshold level for initiating the next action potential. An action potential is a self propagating change in membrane potential that travels along electrically excitable cell membranes and, in this case, causes atrial contraction. The rate

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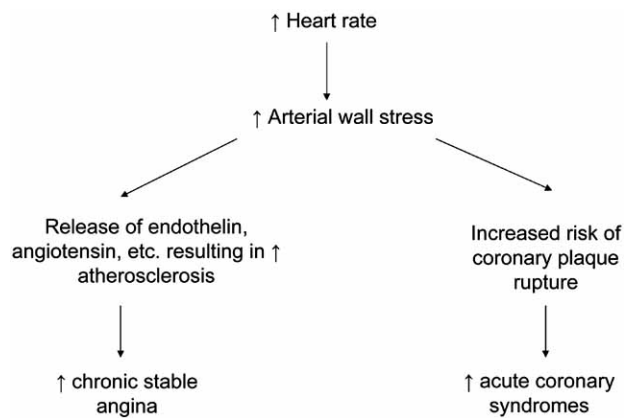


Fig. (2). Clinical cardiovascular effects of increase heart rate.

and timing of depolarization determines the time taken to reach the threshold level and thus determines heart rate (Fig. 3).

The mechanism of spontaneous generation of the pacemaker current is complex and involves at least 6 ionic currents, the I_K , I_f , I_{NaCa} , I_p , I_{CaT} and I_{CaL} . The rate of depolarization is determined primarily by the I_f , I_{CaT} and I_{CaL} channels. Unlike other cardiac cells the depolarizing current is carried primarily by relatively slow, inward Ca^{++} currents instead of fast Na^+ currents. SA nodal action potentials are divided into three phases (phase 4, phase 0 and phase 3 respectively). Phase 4 is the spontaneous depolarization (pacemaker potential) that triggers the action potential once the membrane potential reaches threshold between -40 and -30 mV. Phase 0 is the active depolarization phase of the action potential. Phase 3 is repolarization. Once the cell is completely repolarized at about -70 mV, the cycle is spontaneously repeated.

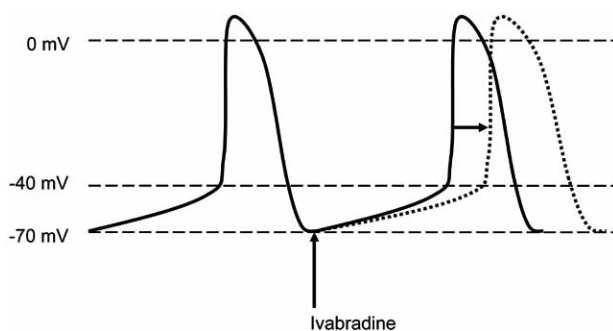


Fig. (3). Effect of ivabradine on pacemaker cell depolarization.

The changes in membrane potential during the different phases are secondary to alterations in the movement of ions (principally Ca^{++} and K^+ , and to a lesser extent Na^+) across the membrane. These ions move through channels that open and close at different times during the action potential.

At the end of repolarization, when the membrane potential is very negative (about -70 mV), ion channels open that conduct slow, inward (depolarizing) Na^+ currents. These channels are called "funny" channels and abbreviated as " I_f ". These depolarizing currents cause the membrane potential to begin to spontaneously depolarize, thereby initiating Phase 4.

As the membrane potential reaches about -50 mV, another type of channel opens. This channel is called transient or T-type Ca^{++} channel. As Ca^{++} enters the cell through these channels the inward Ca^{++} currents further depolarize the cell. As the membrane continues to depolarize to about -40 mV, a second Ca^{++} channel opens. These are the so-called long-lasting, or L-type Ca^{++} channels. Opening of these channels causes more Ca^{++} to enter the cell and to further depolarize the cell until an action potential threshold is reached (usually between -40 and -30 mV). During Phase 4 there is also a slow decline in the outward movement of K^+ as the K^+ channels responsible for Phase 3 continue to close. This fall in K^+ contributes to the pacemaker potential.

Phase 0 depolarization is primarily caused by increased Ca^{++} conductance through the L-type Ca^{++} channels that began to open toward the end of Phase 4. The "funny" currents, and Ca^{++} currents through the T-type Ca^{++} channels, decline during this phase as their respective channels close.

Repolarization occurs (Phase 3) as K^+ channels open thereby increasing the outward hyperpolarizing K^+ currents. At the same time, the L-type Ca^{++} channels close, and the inward depolarizing Ca^{++} currents diminish. Therefore, the action potential in SA nodal cells is primarily dependent upon changes in Ca^{++} and K^+ conductance.

MODIFYING PACEMAKER ACTIVITY

Although pacemaker activity is spontaneously generated by SA nodal cells, the rate of this activity can be modified significantly by external factors such as autonomic nerves, hormones, drugs, ions, and ischemia/hypoxia. The mechanisms and side-effects of well established and novel drug therapies are outlined below.

ESTABLISHED HEART RATE LOWERING DRUGS

The most commonly used heart rate reduction therapies are beta-adrenergic receptor antagonists (beta-blockers) and rate limiting calcium channel blockers (diltiazem and verapamil).

Beta-Blockers

Beta-blockers reduce heart rate by reducing the activity of adenylate cyclase, thus reducing available cAMP. They are of proven benefit in patients with stable angina [10], unstable angina [11], myocardial infarction [3] and heart failure [4,5]. Unfortunately beta-blockers are contra-indicated in certain patient groups such as those with asthma, or with critical limb ischaemia. Beta-blockers also have a significant number of adverse effects including bronchospasm, lethargy, hypotension, worsening of AV node disease, sleep disturbance and depression and are therefore not suitable for use in a significant number of patients.

Calcium Channel Blockers

Rate limiting calcium channel blockers (diltiazem and verapamil) reduce heart rate by direct action on the depolarizing ion currents in pacemaker cells (I_{CaT} and I_{CaL} channels). Both rate-limiting and dihydropyridine calcium channel blockers have morbidity benefits for patients with stable angina [12,13]. Due to their negative inotropic calcium channel blocking effects, they should generally be avoided in patients

with heart failure [14] although amlodipine may be used safely in patients with angina and heart failure [15]. Calcium channel blockers also have several side effects including facial flushing, peripheral oedema and headache which many patients find intolerable.

NOVEL HEART RATE LOWERING DRUGS

Ivabradine - I_f Channel Blocker

As described above the use of both beta-blockers and calcium channel blockers is limited in a significant proportion of patients by contraindications and side effects. The development of I_f channel blockers, as novel heart rate lowering agents represents an exciting new chapter in the treatment of stable angina and may also be useful in unstable coronary syndromes and heart failure.

HOW DOES IVABRADINE WORK?

'Funny' Channels

The I_f channel, first described in 1979, has recently been the focus of intense research as one of the more important ion channels in terms of heart rate control. It is a hyperpolarization-activated, cyclic nucleotide-gated (HCN) channel, of which there appear to be 4 isoforms. The expression of these isoforms appears to change during development, disease states and in response to certain drugs. The I_f channel is a mixed Na⁺-K⁺ inward current which is activated by hyperpolarization and is named 'f' (funny) due to these unusual characteristics. It has slow activation kinetics and opens and closes in response to voltage changes and intracellular cyclic adenosine monophosphate (cAMP) concentrations. Binding of cAMP to the I_f channel encourages it to be open and vice versa. Adrenergic agonists increase cAMP concentrations whereas cholinergic agents decrease cAMP concentrations thereby increasing and decreasing heart rate respectively.

The I_f channel can only be blocked when it is open and its block is favoured by depolarization, thus it is more likely to work when the heart rate is high [19]. The magnitude of I_f inhibition is directly proportional to the frequency of channel opening. This is a particularly useful feature for a heart rate limiting drug as it is more effective at higher heart rates, however, *in vitro* and *in vivo* studies have shown that ivabradine reduces resting heart rate as well as heart rate during exercise without affecting other haemodynamic parameters [20,21].

Selective Heart Rate Reduction

Inhibition of I_f channels in order to decrease the rate of pacemaker cell diastolic depolarisation became an interesting target for potential bradycardic agents. The compound (+/-)-S 15544 was found to act on the I_f channel and reduce the action potential firing rate. The latter compound has two isomers, (+)-S 16257 and (-)-S 16260. These isomers were investigated for their potential to specifically induce bradycardia [17]. Both isomers were shown, *in vitro* and *in vivo*, to have the same bradycardic effects as a result of decreasing the slope of diastolic depolarisation in pacemaker cells. However, prolongation of the action potential was also seen with the isomer (-)-S 16260 and *in vivo* this isomer caused a significant increase in the QTc duration. The (+)-S 16257

has no effect on the QTc. Isomer (+)-S 16257 was therefore developed as ivabradine as it had the desired negative chronotropic effects without the potentially pro-arrhythmic effect of prolonging the QTc interval.

Ivabradine is therefore a selective and specific I_f channel inhibitor. It reduces the 'firing rate' of pacemaker cells without affecting the duration of the action potential [16,17] and acts at concentrations that have no effect on other ionic currents [18] (Fig. 3).

Pharmacokinetics and Pharmacodynamics

Ivabradine has several metabolites for which sensitive and specific chromatographic assays have been developed [22]. The primary active metabolite is N-desmethyivabradine (S 18982) [22]. In humans, following oral administration of ivabradine, plasma levels of both the parent compound (S 16257) and the active metabolite (S 18982) peak between 60 and 90 minutes with a monoexponential fall thereafter [22-24]. The metabolite/parent compound AUC ratios were between 30 and 50% for repeated oral administration of either the 10mg or 20mg dose [24]. Following repeated doses there does not appear to be any accumulation of the parent compound [24]. Clearance of ivabradine is 80% metabolic and 20% renal [25]. This metabolic clearance involves CYP3A4 and therefore raises the possibility of interaction with other cytochrome P450 inducers/inhibitors. However, a randomized, open-label pharmacokinetic trial has shown there is no significant interaction with the commonly prescribed proton pump inhibitors lansoprazole and omeprazole [25].

In healthy volunteers the pharmacodynamic effect of ivabradine has been examined with simultaneous sampling of ivabradine and its active metabolite [24]. Exact pharmacodynamic profiling of the metabolite would require direct administration of this compound however, because the metabolite/parent drug plasma ratio changes over time, certain inferences may still be made with administration of the parent drug alone. A maximum decrease in exercise heart rate of the order of 18% and 27% has been seen with 10mg and 20mg twice daily doses respectively [24]. The initial rapid bradycardic activity of ivabradine appears to be associated with the metabolite but the subsequent long duration of action caused by the parent drug [24].

IVABRADINE STUDIES

Ivabradine is the first I_f channel inhibitor to be launched for clinical use although others are in development. The initial results of clinical trials with ivabradine are promising.

Animal Studies

The initial animal studies of ivabradine demonstrated that ivabradine reduces the rate of spontaneous firing in the isolated rabbit sinoatrial (SA) node by 24% [26]. This bradycardic action is associated with a decrease in the rate of diastolic depolarization without alteration of the action potential amplitude and only a minor increase in its duration [26]. In association with its selective effect on diastolic depolarisation, ivabradine is highly specific for the I_f channel. It reduces the I_f current by approximately 60% without affecting

T-type calcium, L-type calcium and or delaying outward potassium currents [27].

Ivabradine was as effective as betablockade (propranolol) at reducing tachycardia during exercise and reducing ST-segment shift in a porcine model [28]. Unlike propranolol, ivabradine did not reduce left ventricular contractility and it preserved systolic fractional shortening to a greater extent in the ischaemic region. In a model of ischaemic left ventricular dysfunction in dogs, recovery of contractility was quicker in the ivabradine group than the atenolol group [29,30].

Selective inhibition of I_f channels does not appear to be associated with the inherent negatively inotropic effects of beta-blockers. Colin and colleagues demonstrated, in canines, that heart-rate lowering with ivabradine in a dose dependent fashion, was associated with an increase in the duration of diastole and reduced myocardial oxygen consumption [31]. There was a linear relationship between heart rate and myocardial oxygen consumption. This was not observed in the atenolol group where the negatively inotropic effect led to a prolonged ejection time, and consequently a smaller increase in diastolic time, for the same reduction in heart rate [32].

In a rat model the effects of ivabradine on heart rate reduction in the presence of LV dysfunction were assessed [33]. In the group administered ivabradine a dose-dependent reduction in heart rate was observed without modification of systemic haemodynamics. Cardiac output was preserved despite the reduction in heart rate because of a compensatory increase in stroke volume. This increase in stroke volume is most likely due to prolonged diastolic filling. Left ventricular end-systolic diameter was noted to decrease without any modification in LV end-diastolic volume. Following withdrawal of ivabradine, and once heart-rate was comparable to that of the placebo group, there was no significant change in the LV end systolic diameter, function, or stroke volume. This supports the theory that a structural change must take place, in addition to heart rate reduction, in order to account for these results. It has been shown that there is a reduction in the collagen accumulation and an increased capillary density in the ivabradine-treated animals [34].

Clinical Studies

Chronic Stable Angina

The first selective SA node inhibitor to be tested clinically as an antianginal was zatebradine. Initial results were promising but in clinical trials, at doses sufficient to cause a modest reduction in heart rate, there was no prevention of anginal symptoms and there was a propensity to visual disturbance [35].

In contrast, ivabradine has been shown to have beneficial therapeutic effects with minimal side effects. The first of these studies was a randomized, placebo-controlled, double-blind, multi-centre, multinational study of 360 patients with stable angina and documented coronary artery disease [20]. Patients were randomized to receive ivabradine (2.5, 5 or 10mg twice-daily) or placebo for 2 weeks. This was followed by an open-label 2 or 3 month extension on ivabradine 10mg twice daily and a 1-week randomized withdrawal to

ivabradine 10mg twice daily or placebo. The end-points were time to 1mm ST depression and time to limiting angina during exercise tolerance testing. There was a significant improvement in both end-points in the ivabradine group ($P<0.005$ and 0.05 respectively). In the withdrawal period there was deterioration in all exercise parameters in the group that received placebo compared with the group that received ivabradine 10mg twice daily. The only plausible pharmacological explanation for these results was heart rate reduction. Heart rate reduction averaged 12-14 bpm, blood pressure was not affected. The only significant reported side-effect was visual disturbance (a transient brightness called phosphenes) which appeared to be dose-dependent. Phosphenes tended to be non-troublesome, rarely sufficient to cause withdrawal from the study and readily reversible on drug cessation.

Ivabradine has also been compared to established anti-anginal therapies. Tardif *et al.* [21] reported the non-inferiority of ivabradine in comparison with atenolol. This was a randomized double-blind study which compared ivabradine with atenolol over 4 months in 939 patients with stable angina and documented coronary artery disease. Patients received either ivabradine 5mg twice daily for 4 weeks, increased to 7.5mg twice daily for a further 3 months, or atenolol 50mg once daily for 4 weeks increased to 100mg once daily for a further 3 months. At 4 months the treadmill exercise duration had increased by 86.8 seconds with ivabradine 7.5mg twice daily and by 78.8 seconds in the atenolol 100mg once daily group. Non-inferiority was seen for all end-points of time to limiting angina, time to angina onset and time to 1mm ST depression ($P<0.0001$). Once again the most significant side-effect seen was visual disturbance and was of a similar rate to that seen in the study by Borer *et al.* [20].

Ivabradine has more recently been compared to amlodipine in the prevention of stable anginal symptoms [36]. This was a multi-centre randomized, double-blind, three-arm parallel group trial involving 1195 patients with stable angina and documented coronary artery disease. Patients were randomized to receive ivabradine 7.5mg twice daily, 10mg twice daily or amlodipine 10mg once daily for a 3-month period. The primary end-point was the change in total exercise duration between baseline and 3 months; secondary end-points were time to anginal symptoms, time to 1mm ST depression, and use of short-acting nitrates. Non-inferiority was shown for all end-points ($P<0.001$). In this study visual side-effects led to patient withdrawal in 0.8% ($n=6$) of the ivabradine group, while 1.5% ($n=6$) of patients in the amlodipine group withdrew because of problems with peripheral oedema.

Heart Failure

The potential therapeutic effects of a specific heart rate lowering agent in the presence and treatment of LV dysfunction has been assessed in animal studies. Manz *et al.* [37] have shown a benefit from heart rate reduction without a deleterious effect on myocardial contractility in this setting.

The BEAUTIFUL trial [38] is a recently published, large, multicenter, randomized, international, double-blind, pla-

cebo-controlled trial of ivabradine in patients with stable coronary artery disease and left ventricular systolic dysfunction (ejection fraction <40%). Participants were randomized to receive either placebo or ivabradine 5mg twice-daily for 2 weeks increasing to a target dose of 7.5mg twice-daily, in addition to conventional heart failure medications including beta-blockers. The primary end-point was a composite of cardiovascular mortality, admission to hospital with acute myocardial infarction (AMI) or new onset or worsening heart failure. There was no significant difference in the incidence of this endpoint between the two groups however subgroup analysis has suggested benefit in selected patients and raised several new questions. In patients with heart rates greater than 70bpm at baseline, ivabradine reduced the secondary endpoints of admission to hospital with fatal or non-fatal MI by 36% and the need for coronary revascularisation by 30% [39]. This reduction in coronary artery disease outcomes secondary to heart rate lowering is consistent with evidence suggesting that increased heart rates may accelerate the progression of atherosclerosis [40] and decrease diastolic myocardial perfusion time resulting in ischaemia [41]. The lack of association between ivabradine and clinical outcomes in the main study is postulated to have resulted from either insufficient reductions in heart rate or due to very low heart rates at baseline. No subgroup analysis of patients with heart rates less than 70 at baseline has been published. It is reasonable to conclude from the BEAUTIFUL trial that the combination of ivabradine and beta-blockers appears safe and improves coronary artery disease outcomes in patients with stable coronary artery disease, left ventricular dysfunction and heart rates of 70bpm or more.

Acute Coronary Syndromes

There are few published data on the use of ivabradine in acute coronary syndromes but the potential beneficial effects of a pure heart rate limiter in this area have generated a lot of interest. It is theorized that the degree of mechanical stress experienced by an atherosclerotic plaque is the result of foreshortening and twisting of large epicardial arteries during systole, and there is empirical evidence that there is an association between the tendency for plaque rupture and heart-rate [42]. Thus slowing the heart rate should reduce this risk. The recent subgroup analysis of the BEAUTIFUL trial showing specifically improved coronary artery disease outcomes adds weight to this hypothesis however a large randomised trial is required to investigate the value of additional heart rate limiting, by use of ivabradine or other agents, in patients with an acute coronary syndrome.

SELECTIVITY AND SAFETY

Ivabradine is a well-tolerated drug. In clinical studies there is a less than 1% withdrawal rate because of side effects [43]. Importantly, and in contrast to beta-blockers and calcium channel blockers, ivabradine reduces heart rate without affecting myocardial contractility or the conduction system [17]. There is no significant prolongation of the PR, QRS or corrected QT intervals [20,21]. It also reduces heart rate in a predictable fashion (by 10-12 bpm). In the reported clinical trials there have been few problems with drug-induced bradycardia and minimal patient withdrawal for this

reason [20,21]. The most frequently observed side effect was visual disturbance. This is an unpredictable adverse effect. The retinal I_h channel, which is similar in structure to the I_f channel, acts to curtail retinal response to light. Thus, blockage of the I_h by ivabradine can produce transient enhanced brightness in a limited visual field area, an effect called phosphenes [43]. It may be induced by rapid changes in light intensity and appears to be a dose-dependent effect. In clinical studies less than 1% of patients withdrew because of side effects. This interesting interaction with the I_h channel was generally seen within the first two months, was well tolerated, and in the majority of patients resolved during treatment and in all others following cessation of the drug. Of practical importance, the European regulatory authorities have not deemed phosphenes to pose a significant driving risk [43]. A more recent review has confirmed the safety of ivabradine although post marketing surveillance continues [44].

CLINICAL CONSIDERATIONS

If a patient develops a significant bradycardia then care should be taken when administering ivabradine. If a patient develops significant hypotension, especially if symptomatic, then ivabradine should be withheld as ivabradine may reduce the ability of the patient to increase their intrinsic heart rate to compensate for a low blood pressure and therefore worsen the hypotension.

A patient who develops atrial fibrillation will gain no rate limiting benefit as ivabradine appears to only affect SA node function and not conduction at the AV node. Thus, in contrast to beta-blockers and rate limiting calcium channel blockers, patients who develop AF while on ivabradine will be relatively less protected from a rapid ventricular response. If a patient develops atrial fibrillation with a rapid ventricular rate while on ivabradine then an alternative anti-arrhythmic should be considered eg beta-blocker, digoxin, amiodarone or rate limiting calcium channel blocker.

Patients who are prescribed ivabradine (for the first time or when a dose increase is implemented) should be warned about visual disturbances and reassured that these are reversible. .

CONCLUSIONS

The major advantage of selective I_f channel blockers is their apparent lack of adverse effects. They are likely to be of most use in patients in whom betablockers are contraindicated or where the negative inotropic and hypotensive effects of beta-blockers or calcium channel blockers are undesirable. Ivabradine improves exercise tolerance and time to developing ischaemia during exercise in patients with chronic stable angina. In addition the combination of ivabradine and beta-blockers appears safe and improves coronary artery disease outcomes in patients with stable coronary artery disease, left ventricular dysfunction and heart rates of 70bpm or more. Further studies are required to define if there is an optimal degree of heart rate lowering in this patient population. We await with interest, trials of ivabradine or other I_f channel blockers in the setting of acute coronary syndromes.

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