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# Clinical Results of $I_f$ Current Inhibition by Ivabradine

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## Abstract

Heart rate reduction is a well accepted and effective approach for the prevention of angina pectoris. Ivabradine is the first selective and specific inhibitor of the $I_f$ current and provides pure heart rate reduction without altering myocardial contractility. Clinical evidence of the antianginal and anti-ischaemic efficacy and tolerability of ivabradine comes from the largest clinical development programme that has ever been performed in stable angina pectoris, involving more than 5000 patients. Ivabradine at the dosages of 5 or 7.5mg twice daily is as effective as reference antianginal approaches such as β-adrenoceptor antagonists and calcium channel antagonists. The clinical efficacy and safety of ivabradine has also been confirmed in a 1-year follow-up study. Ivabradine is well tolerated and free from the most commonly observed adverse effects of currently prescribed antianginal drugs. Visual symptoms can occur in a minority of patients treated with ivabradine and are not associated with structural ocular changes. The ongoing clinical development programme with the two major morbidity-mortality studies, BEAUTIFUL and SHIfT, has the potential to greatly extend the use of ivabradine in patients with coronary artery disease as well as in those with heart failure.

Stable angina pectoris (SAP) is a disabling disorder. Its management continues to be a major challenge in cardiology. As the presenting symptom in approximately 50% of patients with coronary heart disease (CHD),[1] chronic SAP remains a major burden on public health. In Europe and the US, 30 000–40 000 per million people experience chronic SAP.[2,3]

Angina results when myocardial perfusion is insufficient to meet metabolic demand. Heart rate (HR) is one of the most important determinants of myocardial oxygen demand. However, increases in HR exacerbate myocardial ischaemia and subsequent angina not only because of the increase in myocardial oxygen demand but also because, as HR increases, myocardial perfusion decreases because of shortening of the duration of diastole. The incidence of ischaemic episodes doubles when the HR increases from 60 to 80 beats/min.[4] In addition to the reduction in myocardial ischaemia achieved with lowering HR, emerging data suggest that HR is also an independent predictor of cardiovascular morbidity-mortality.[5-8]

The benefits of HR reduction are among the primary bases for use of β-adrenoceptor antagonists (β-blockers), verapamil and diltiazem-type calcium channel antagonists in SAP.[9,10] Recent advances in understanding sinus node activity encouraged the novel therapeutic concept of pure HR reduction. $I_f$, a mixed $Na^+$-$K^+$ inward current activated by hyperpolarisation and modulated by the autonomic nervous system, is one of the most important ionic currents

for regulating pacemaker activity in the sinoatrial node. Ivabradine is a novel, specific HR-lowering agent, which acts in sinoatrial node cells by selectively and specifically inhibiting the pacemaker $I_f$ current in a dose-dependent manner. It slows the diastolic depolarisation slope of the action potential of sinoatrial node cells and reduces HR.[11,12] The benefits of HR reduction with ivabradine and its clinical implications have so far been demonstrated in a clinical development programme that involved around 5000 patients with CHD and chronic SAP. Ongoing clinical trials involve more than 10 000 additional patients.

## 1. Ivabradine and Heart Rate Reduction

In a randomised, double-blinded, multicentre, multinational trial involving 360 patients randomised to placebo or to one of three dosages of active therapy (2.5, 5 or 10mg twice daily), ivabradine consistently reduced HR at rest and during exercise.[13] The magnitude of HR reduction was slightly smaller than that expected with therapeutic doses of β-blockers and greater than that with calcium channel antagonists like verapamil and diltiazem. HR reduction with ivabradine was dose related and was observed across all dosages (figure 1). Despite substantial HR lowering, ivabradine caused little change in blood pressure relative to placebo.

The HR reduction obtained with ivabradine correlates with pretreatment HR in the clinical setting. This was studied in 1328 patients with documented stable CHD treated with ivabradine 5, 7.5 or 10mg twice daily. Inverse linear correlations between pretreatment HR and changes in HR during treatment were observed for all three dosages of ivabradine (coefficients of correlation, r = −0.54 to −0.57) [figure 2]. Thus, the HR-reducing effect of ivabradine was smaller in patients with the lowest baseline HR and more pronounced in patients with higher HR. This explains the low incidence of bradycardia observed in clinical trials at the therapeutic dose of 7.5mg twice daily, even in patients who had a low baseline HR.[14]

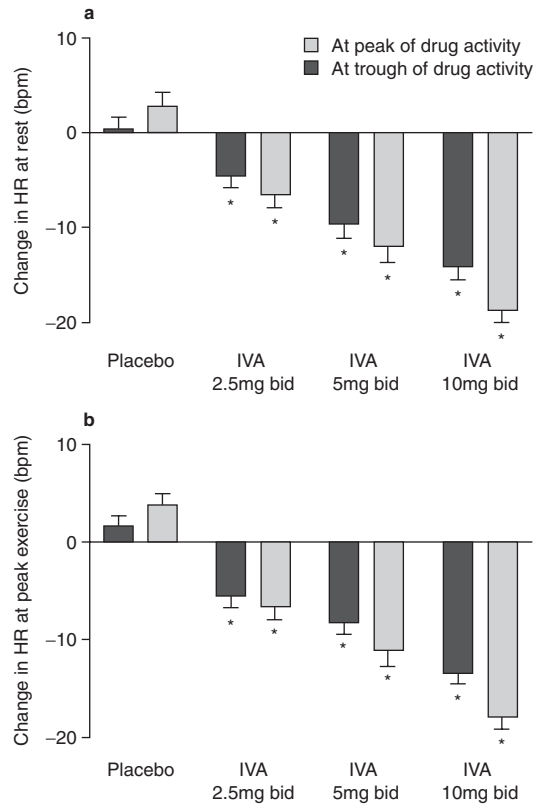


**Fig. 1.** Changes in heart rate [HR] (**a**) at rest and (**b**) at peak exercise in the different treatment groups during double-blinded dose-ranging of ivabradine (IVA) given twice daily (bid). Error bars, standard error of the mean. Reproduced from Borer et al.,[13] with permission. * $p \leq 0.05$ vs placebo in pair-wise comparison.

## 2. Antianginal Efficacy and Safety of Ivabradine in Patients with Stable Angina Pectoris

### 2.1 Randomised Trials

The initial randomised, double-blind, multicentre, multinational trial in 360 patients used exercise test parameters to compare ivabradine versus placebo at trough plasma drug levels over a 14-day treatment period.[13] Time to 1mm ST-segment depression in the ivabradine 5mg and 10mg groups increased compared with placebo ($p < 0.005$), as did time to limiting angina (10mg: $p < 0.05$). Data from the subsequent open and run-out periods showed that both antianginal and anti-ischaemic benefits

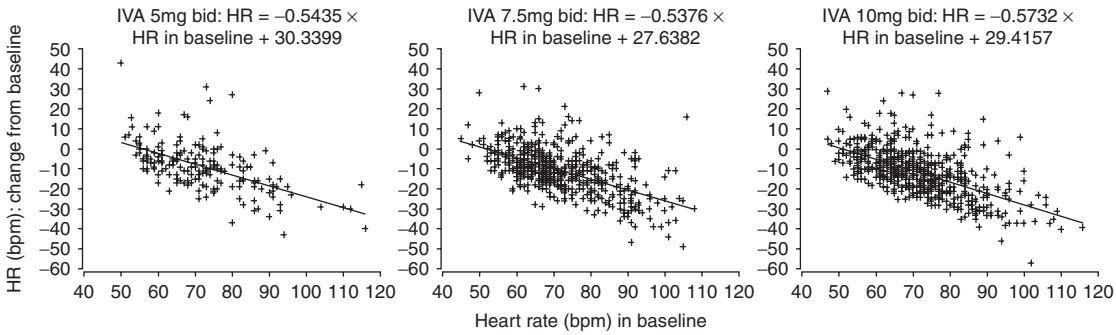


**Fig. 2.** Low incidence of significant bradycardia during therapy with an $I_f$ current inhibitor, ivabradine (IVA): heart rate (HR) reduction depends on baseline HR. Reproduced from Savelieva et al.,[14] with permission. **bid** = twice daily.

persisted without the development of pharmacological tolerance. In addition, mean angina frequency decreased from four per week at baseline to less than one per week at the end of the open-label extension ($p < 0.001$). No rebound phenomena were observed upon treatment cessation.

#### *2.1.1 Ivabradine versus β-Adrenoceptor Antagonists*

In the INITIATIVE (INternatIonal TrIal of the Antianginal effects of IVabradinE compared with atenolol) trial – a 4-month randomised, double-blind, controlled multicentre study of 939 patients with SAP – the non-inferiority of ivabradine 7.5 and 10mg twice daily compared with atenolol 100mg once daily in terms of their antianginal and anti-ischaemic effects was demonstrated for all exercise parameters.[15] Ivabradine increased total exercise duration by 1.5 minutes at the trough of drug activity, and times to limiting angina and angina onset were also improved (figure 3). The increase in time to 1mm ST-segment depression indicates that the improvement in total exercise capacity is associated with a relevant anti-ischaemic effect of ivabradine. When compared with baseline, HR and rate-pressure product (RPP) were reduced at end of treatment at rest by both treatments. The decrease in HR at peak exercise was greater with atenolol (14.0 beats/min) than with ivabradine (8.6–10.3 beats/min with 7.5–10mg). Ivabradine induced a similar or greater improvement in exercise capacity than atenolol for a comparatively smaller reduction in RPP and HR. This greater efficiency in the increase in exercise capacity for every beat of HR reduction may be attributable to the lack of negative inotropic, peripheral vascular or coronary vasoconstrictor effect associated with ivabradine.[16]

#### *2.1.2 Ivabradine versus Calcium Channel Antagonists*

A 3-month randomised trial in 1195 SAP patients demonstrated the non-inferiority of twice-daily ivabradine 7.5mg and 10mg with respect to amlodipine 10mg once daily ($p < 0.001$).[17] Antianginal efficacy was achieved within 1 month of treatment. In all three treatment groups, time to limiting angina and angina onset increased by 0.5 minute and 1 minute, respectively, while time to 1mm ST-segment depression increased significantly by 0.7 minute. In addition, mean weekly angina frequency and short-acting nitrate consumption decreased at study end by two-thirds compared with baseline in all three study groups. HR decreased significantly by 11–13 beats/min at rest and by 12–15 beats/min at peak exercise with ivabradine but did not with amlodipine. RPP, a marker of oxygen requirement of the heart, decreased more with ivabradine than with amlodipine ($p < 0.001$ at rest and at peak exercise).

### 2.2 Long-Term Efficacy of Ivabradine

The longer term efficacy and safety of ivabradine have been established over 1 year in 386 patients with SAP already treated by nitrates or dihydropyridine calcium channel blockers.[18] Two different dosages (5 and 7.5mg twice daily) of ivabradine

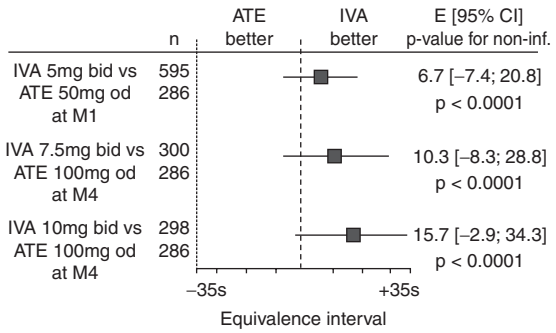


**Fig. 3.** Effects on total exercise duration at trough of drug activity. Reproduced from Tardif et al.,[15] with permission. **ATE** = atenolol; **bid** = twice daily; **E** = estimate; **IVA** = ivabradine; **M1** = 1 month; **M4** = 4 months; **non-inf.** = non-inferiority; **od** = once daily.

were used in that study. Ivabradine was shown to reduce HR by 10 beats/min at a dosage of 5mg twice daily and 12 beats/min with 7.5mg twice daily. Ivabradine maintained this HR reduction over the year of follow-up (figure 4). The number of angina attacks reported by patients was reduced significantly ($p < 0.05$) by the addition of ivabradine.

### 2.3 Clinical Safety of Ivabradine

Ivabradine has demonstrated a very good safety profile throughout its large clinical development programme. The most frequently reported adverse events have been visual symptoms, the majority being phosphenes that were transient and non-serious in nature. These consisted of transient enhanced brightness in limited areas of the visual field that were commonly associated with abrupt changes in light intensity. The visual symptoms were dose dependent and generally mild and well tolerated, causing 1% of patients to withdraw from treatment. They may be related to the action of ivabradine at hyperpolarisation-activated, cyclic nucleotide-gated cation current channels known to be present in the retina and similar, though not identical, to those in the sinoatrial node. All visual symptoms resolved spontaneously during therapy or after drug discontinuation and did not lead to permanent retinal damage.

Bradycardia sufficient to be reported as an adverse event was apparent in 2.2% of patients treated with ivabradine 7.5mg twice daily, despite the primary HR-lowering action of the drug. The explanation lies in the direct rate-related dynamics of the HR-lowering effect (use-dependence mechanism), which limit the risk of excessive bradycardia in patients with an initially low HR. Electrocardiographic QT intervals from all patients enrolled in the ivabradine development programme were evaluated using a population-corrected formula. Absence of change in the corrected QT interval throughout the follow-up period provides strong evidence that ivabradine has no significant direct effect on the duration of ventricular repolarisation.[19] Importantly, the abrupt discontinuation of ivabradine has not resulted in a rebound of angina to frequencies greater than those seen before drug initiation.

In summary, the clinical tolerability of ivabradine was documented in a large population of patients with CHD and SAP, and drug-related adverse events had minimal impact on acceptability.

## 3. Possible Long-Term Morbidity and Mortality Benefits of Ivabradine

A considerable amount of epidemiological and experimental evidence indicates a relationship between elevated HR and the development and progression of coronary atherosclerosis.[20-23] The association between high HR and morbidity/mortality has been found not only in patients with CHD, but also in the general population and in patients with myocardial infarction, congestive heart failure, hypertension or diabetes mellitus.[5-7,24,25] In addi-

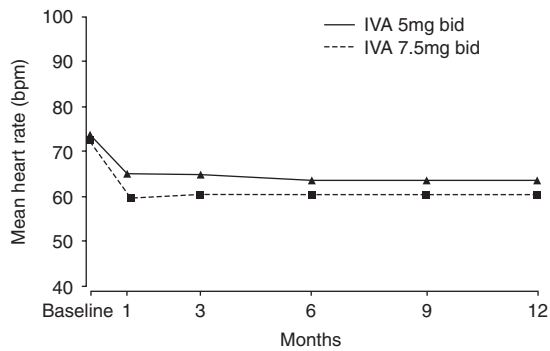


**Fig. 4.** Heart rate reduction maintained over a 1-year treatment with ivabradine (IVA). Reproduced from Lopez-Bescos et al.,[18] with permission. **bid** = twice daily.

tion, pharmacological HR slowing obtained with β-blockade has been associated with improved survival in clinical trials of patients after myocardial infarction or with congestive heart failure.[26,27] Reversal of β-blocker-induced bradycardia has deleterious effects on ventricular function, suggesting that HR reduction is an important mediator of their effects.[28]

The effects of ivabradine on cardiovascular morbidity and mortality are currently being explored in the BEAUTIfUL (morBidity-mortality EvAlUaTion of the $I_f$ inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction) study, a large-scale international randomised trial of more than 10 000 patients.[29] A small pilot placebo-controlled randomised study in 65 patients with CHD and moderate left ventricular systolic dysfunction has suggested that ivabradine may be associated with improved left ventricular remodelling.[30] Ivabradine improved HR variability compared with amlodipine in a subset of 319 patients who underwent ambulatory monitoring at baseline and after 3 months of therapy with ivabradine 7.5mg twice daily (n = 104) or 10mg twice daily (n = 106), or

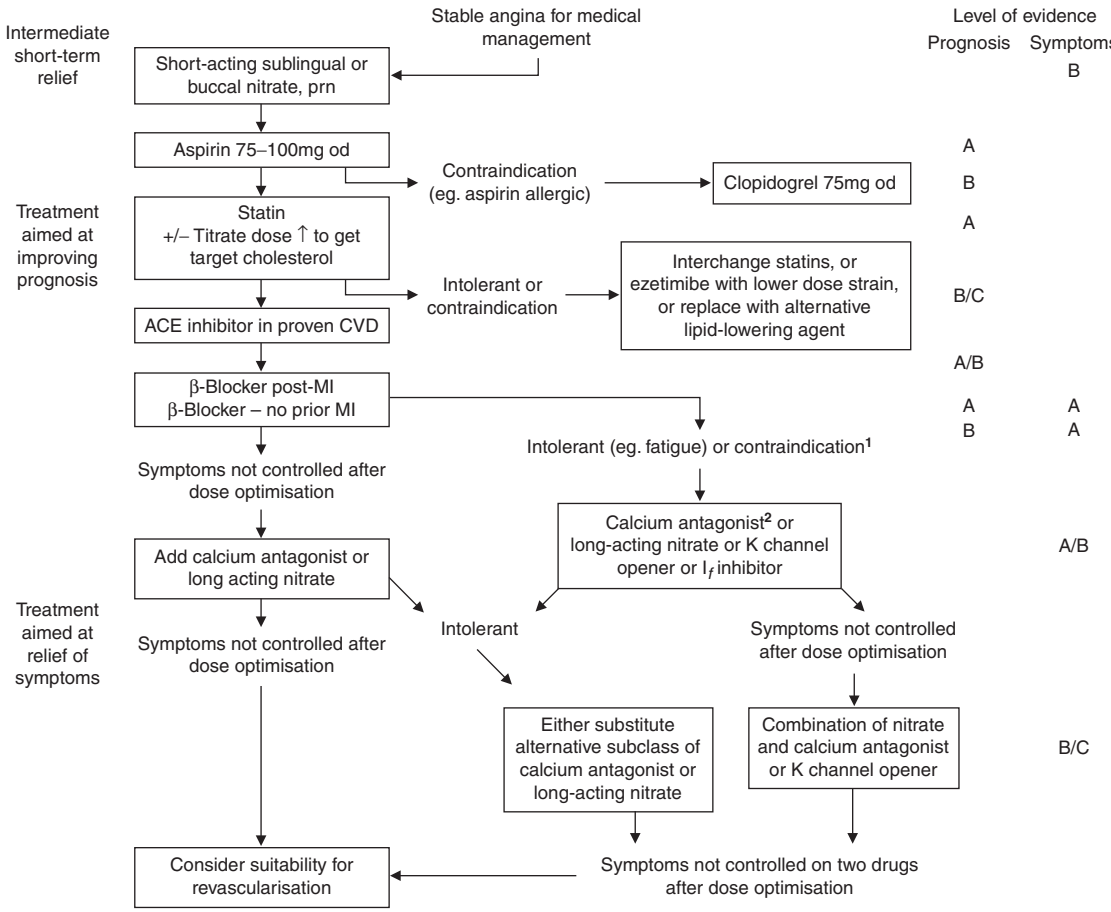


**Fig. 5.** Algorithm for the medical management of stable angina. High-risk candidates for revascularisation on prognostic grounds alone should be identified and referred appropriately (reproduced from European Society of Cardiology,[35] with permission). **1** Relative contraindications to β-blockade include asthma, symptomatic peripheral vascular disease, and first-degree heart block; **2** Avoid short-acting dihydropyridine formulations when not combined with β-blocker. **CVD** = cardiovascular disease; **MI** = myocardial infarction; **od** = once daily; **prn** = as needed; ↑ indicates increase.

amlodipine 10mg once daily (n = 109).[31] Reduced HR variability is a marker of impaired autonomic nervous system activity and is associated with increased all-cause and cardiovascular death.[32] The BEAUTIfUL study will test whether these potentially favourable effects obtained with ivabradine will translate into actual reduction in morbidity and mortality in CHD patients with associated left ventricular dysfunction.

## 4. Current Clinical Role for Ivabradine

HR-lowering in patients with CHD is likely to reduce myocardial ischaemic episodes. Given the current data on its efficacy and safety, there appears to be a significant role for ivabradine in the management of patients with CHD. The efficacy of ivabradine does not appear to be reduced in patient populations in whom other antianginal agents may be either relatively contraindicated or less well tolerated (e.g. patients with diabetes mellitus or asthma, and the elderly). Ivabradine does not interfere with respiratory function. A randomised double-blind, placebo-controlled, crossover study assessed the effects of ivabradine (10mg twice daily for 5 days) on lung function (peak expiratory flow rate [PEFR] and forced expiratory volume in 1 second) in 20 stable asthmatic patients.[33] Ivabradine did not have an effect on the PEFR during the 5 days of treatment. Asthma symptoms or rescue medication use were also not different between the ivabradine and placebo groups.[33] Another study has shown that ivabradine is not associated with detrimental effects on blood glucose and glycated haemoglobin levels in diabetic patients.[34] Thus, ivabradine can be used for the treatment of stable patients with CHD and angina who are intolerant or have contraindications to β-blockers. It is also a logical addition for the treatment of angina pectoris when symptoms are not controlled by previous antianginal medications. The role of $I_f$ inhibitors like ivabradine is outlined in the recent algorithm for the medical management of SAP described by the European Society of Cardiology (figure 5).[35]

Finally, the ongoing clinical development programme with two major morbidity-mortality studies (BEAUTIfUL and SHIfT [Systolic Heart failure treatment with the If inhibitor Ivabradine Trial]) has the potential to greatly extend the use of ivabradine in cardiology. The BEAUTIfUL study is evaluating the morbidity and mortality benefits of ivabradine in CHD patients with associated left ventricular dysfunction, while the SHIfT study is designed to evaluate the superiority of ivabradine over placebo in the reduction of cardiovascular mortality and hospitalisations for worsening heart failure in patients with moderate to severe chronic heart failure and left ventricular systolic dysfunction, who are already receiving 'appropriate' therapy at 'optimal' dosages.

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