



# Coronary artery disease management with ivabradine in clinical practice

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## KEYWORDS

Coronary artery disease;  
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Ivabradine;  
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The presence of limiting angina can have a profound impact on the quality of life of patients with stable CAD, and may affect prognosis. Limiting angina symptoms are independently predictive of adverse outcomes. The aims of treating angina are to minimize or abolish symptoms and/or ischemia and to improve prognosis. Elevated HR plays an important role in the development and progression of coronary atherosclerosis, triggering ischemic events through an increase in myocardial oxygen demand and a reduction in diastolic perfusion. Reducing the HR can reduce the symptoms as well as improve the prognosis as shown in Beautiful trial. Ivabradine, a specific inhibitor of the  $I_f$  current in the sinoatrial node, resulting in heart rate reduction, is currently indicated for the treatment of chronic stable angina in CAD patients with a contraindication or intolerance to beta-blockers or in combination with beta-blockers in patients inadequately controlled and whose HR is above 60 bpm. In patients with a contraindication to beta blockers, ivabradine remains a preferred option as it has a well-documented anti-ischemic and antianginal efficacy through HR slowing at least comparable to that of beta-blockers, along with an excellent safety and tolerability. Therefore, ivabradine represents an important addition to the current options of different anti-ischemic agents that are available, with an impact in symptom relief as well as patient outcome.

Despite therapeutic advances, cardiovascular diseases remain a major cause of morbidity and mortality in Western countries, and constitute a leading public health problem and a considerable economic burden in Europe.<sup>1</sup>

Coronary artery disease (CAD) is a chronic progressive disease that may remain clinically stable but can also rapidly progress to acute coronary syndromes or sudden death precipitated by plaque rupture or erosion. Angina pectoris is the presenting symptom of CAD in 50% of cases.<sup>2</sup> Epidemiological data show that in the general population the prevalence of stable angina ranges between 20 000 and 40 000 per 1 million people<sup>3</sup> and sharply increases with age.<sup>4</sup> The presence of limiting angina can have a profound impact on the quality of life of patients with stable CAD and may affect prognosis.

The increased risk of mortality in patients with limiting angina appears to be comparable to a decade of age difference, the presence of diabetes, or the presence of heart failure.<sup>5</sup>

Limiting angina symptoms have been found to be independently predictive of adverse outcomes, with a substantial increase in risk for every change in the Canadian Cardiovascular Society (CCS) classification.<sup>6</sup> Thus, the aim of treating angina is two-fold: to minimize or abolish symptoms and/or ischaemia and to improve the prognosis.<sup>3</sup>

## Pivotal role of heart rate reduction in the treatment of CAD

Heart rate (HR) is one of the principal determinants of myocardial oxygen consumption, and elevated HR is a

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state where the myocardial oxygen demand is increased. Elevated HR shortens the length of each cardiac cycle, thereby reducing diastolic perfusion time and oxygen supply. Elevated HR also appears to have an impact on the development of atherosclerosis via an increase in the exposure of endothelium to low shear stress at higher HR.<sup>7</sup> Also, increase of HR may increase the risk of acute coronary syndromes because of excessive mechanical stress on the atherosclerotic plaque.<sup>8</sup> Therefore, elevated HR potentially plays an important role in the development and progression of coronary atherosclerosis, triggering ischaemic events through an increase in myocardial oxygen demand and a reduction in diastolic perfusion. Thus, exclusively reducing the HR could reduce the symptoms as well as improve the prognosis, thereby meeting both the objectives of treating angina patients.

### Treating CAD by specific HR reduction

Ivabradine is a novel, specific HR-lowering agent which acts in the sinoatrial node cells by selectively and specifically inhibiting the pacemaker  $I_f$  current in a dose-dependent manner.<sup>9</sup> It reduces HR while preserving the force of contraction, cardiac conduction, and blood pressure. This specific HR reduction with ivabradine leads to antianginal and anti-ischaemic efficacy and improvement of prognosis.

The first large-scale study of ivabradine was an international, multicentre, double-blind trial in which 360 patients with a history of chronic stable angina were randomized to placebo or ivabradine. Ivabradine dose dependently reduced HR and this was associated with a significant increase in the time to 1-mm ST-segment depression and the time to limiting angina.<sup>10</sup>

These encouraging results compared with placebo supported the rationale of testing ivabradine vs. other antianginal anti-ischaemic drugs, particularly beta blockers. The International Trial of the Antianginal effects of Ivabradine compared with atenolol compared the anti-ischaemic and antianginal efficacy of ivabradine 7.5 mg and atenolol 100 mg od in 939 stable angina pectoris patients.<sup>11</sup> After 4 months of treatment, the decrease in HR at rest was similar to atenolol 100 mg od (15.6 b.p.m.) and ivabradine 7.5 mg bid (14.3 b.p.m.), whereas the improvement in exercise duration was greater with ivabradine 7.5 mg bid. This highlights that ivabradine probably has other effects, for example, preservation of coronary artery dilatation during exercise and greater duration of diastole, which contribute to the greater HR efficiency. Thus for the same HR reduction, the increase in exercise duration with ivabradine 7.5 mg bid is twice than that with atenolol 100 mg od.<sup>11</sup>

The anti-ischaemic efficacy of ivabradine in combination with beta-blocker therapy was investigated in a 4-month study of 889 stable angina patients already receiving atenolol 50 mg/day.<sup>12</sup> Patients were randomly assigned to treatment with ivabradine 5 mg bid uptitrated to 7.5 mg bid after 2 months ( $n = 449$ ), or to placebo ( $n = 440$ ) in addition to the beta blocker. In the

ivabradine group, 90% of patients were uptitrated to 7.5 mg bid. The baseline resting HR in these patients was 67 b.p.m. Ivabradine reduced the baseline HR by 9 b.p.m. at the end of the study and this reduction was associated with a statistically significant improvement in all exercise test parameters when recorded at trough of activity at the end of 4 months.

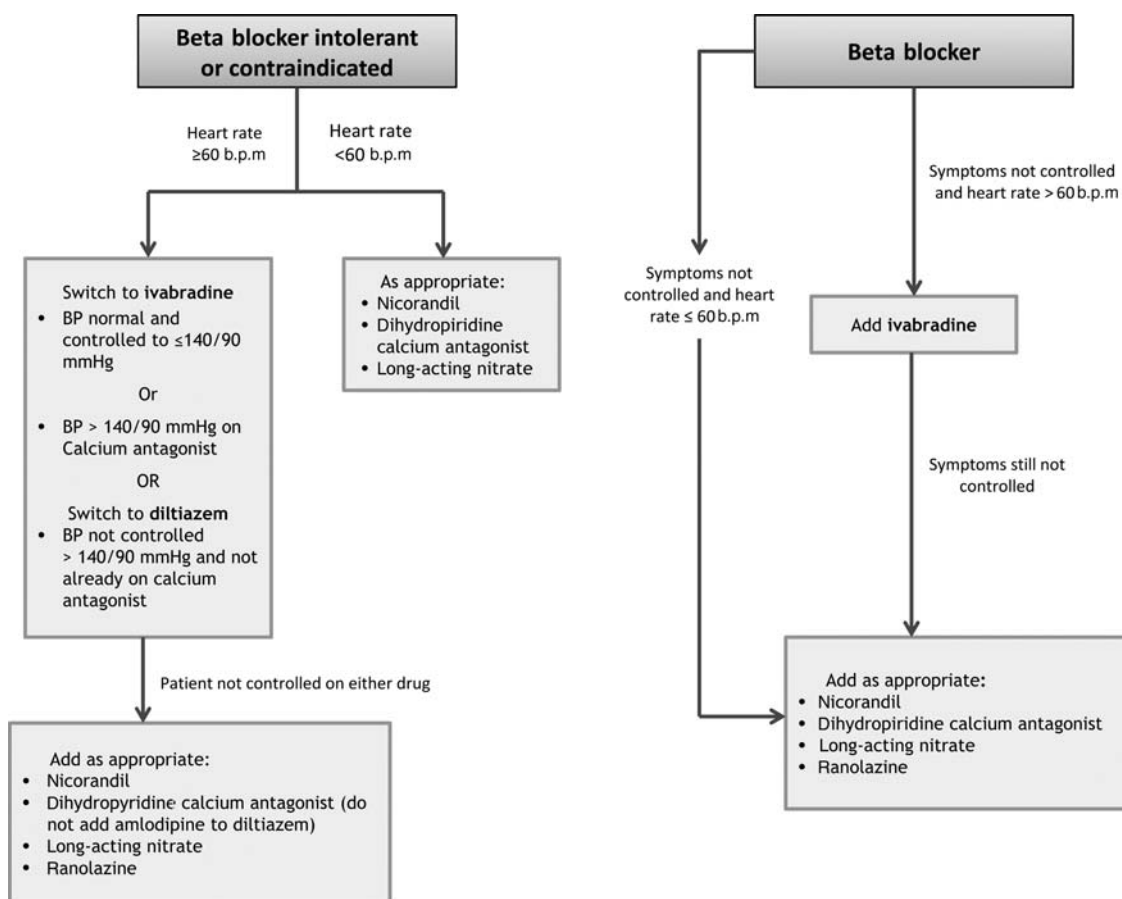
Thus, exclusive HR reduction with ivabradine provides antianginal and anti-ischaemic efficacy in monotherapy and in patients already receiving other antianginal drugs such as beta blockers.

The antianginal and anti-ischaemic efficacy of ivabradine was studied in 29 patients with stable angina and moderate left ventricular systolic dysfunction already being treated with bisoprolol 5 mg od.<sup>13</sup> This pilot study evaluated the addition of ivabradine 5 mg to bisoprolol vs. uptitration of bisoprolol to 10 mg od, in patients with stable angina. The addition of ivabradine resulted in an improvement in exercise capacity, as shown by the results of the 6-min walking distance and exercise tolerance tests, whereas in the bisoprolol group there was no significant improvement in the results of either test.

These findings in controlled studies have been confirmed in a broad patient population in everyday clinical practice. In the REDUCTION study,<sup>14</sup> 4954 patients with stable angina pectoris received ivabradine in everyday routine practice and underwent follow-up for 4 months. In this population of patients with symptomatic CAD, ivabradine reduced the HR and was highly effective: angina pectoris attacks were significantly reduced as was the consumption of short-acting nitrates ( $P < 0.0001$ ). Ivabradine was well tolerated.

### Improving prognosis in angina patients with ivabradine

The prognostic benefits of ivabradine were first assessed in the morbidity-mortality Evaluation of the  $I_f$  inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction (BEAUTIFUL) study.<sup>15</sup> BEAUTIFUL was a randomized, double-blind, parallel-group trial carried out in 781 centres in 33 countries, which included 10 917 patients  $\geq 55$  years of age (or  $\geq 18$  years if diabetic) with documented stable CAD and left ventricular ejection fraction  $< 40\%$  and left ventricular (LV) end-diastolic diameter  $> 56$  mm. Patients were randomized to either ivabradine or matching placebo on top of optimal preventive therapy and were followed up for 19 months. The principal results of the BEAUTIFUL trial provided answers to some very important questions in CAD patients. The BEAUTIFUL study established resting HR  $\geq 70$  b.p.m. as a risk factor for cardiovascular outcomes in patients with stable CAD and LV systolic dysfunction.<sup>16</sup> Although there was no measurable effect of treatment in the overall population, the BEAUTIFUL trial demonstrated that in patients with elevated HR ( $\geq 70$  bpm), ivabradine reduces the risk of fatal and nonfatal myocardial infarction by 36% ( $P = 0.001$ ) and coronary revascularization by 30% ( $P = 0.016$ ). A *post hoc* analysis<sup>17</sup> was



**Figure 1** Symptomatic algorithm to show how heart rate control can lead to symptom control. In guidelines from Fox K, Arden C, Begg A *et al.* *Consensus Guideline for the Management of Symptomatic Stable Angina in Primary Care*. Berkhamsted: MGP Ltd; 2010.

done in 1507 (13.8%) patients who had limiting angina at baseline to evaluate the prognostic benefits of ivabradine. A total of 734 patients were randomized to ivabradine and 773 to placebo, and none were lost to follow-up. Angina was defined according to the NYHA classification. Patients were questioned at the inclusion visit regarding the presence of symptoms limiting activity, and patients in whom the limitation was related to anginal pain were included in this analysis. The reduction in the primary end point of the study (cardiovascular death, myocardial infarction, or hospitalization for heart failure) was 24% in the whole group of patients with limiting angina and 31% in the group with baseline heart rate  $\geq 70$  bpm.

### Place of ivabradine in the management of stable angina

Ivabradine is currently indicated for the treatment of chronic stable angina in CAD patients with a contraindication or intolerance to beta blockers or in combination with beta blockers in patients b.p.m. inadequately controlled and whose HR is  $>60$  b.p.m.. In patients with a contraindication to beta blockers, ivabradine remains a preferred option as it has a well-documented anti-ischaemic and antianginal efficacy through HR slowing

at least comparable to that of beta blockers, along with an excellent safety and tolerability profile.<sup>11</sup> Moreover, in routine clinical practice, stable angina may not be controlled with one drug alone. Though combination therapy is recommended to improve symptomatic management, most clinical studies have demonstrated only modest improvement in exercise tolerance test parameters compared with monotherapy at the peak of drug activity, with no significant differences 6 h after drug intake.<sup>18</sup> These findings and the results of the ASSOCIATE study,<sup>12</sup> which demonstrate the antianginal and anti-ischaemic efficacy of ivabradine in combination with beta blockers, even at the trough of drug activity, suggest that ivabradine should preferentially be used in combination with beta blockers (*Figure 1*). Thus in clinical practice ivabradine could be used for angina patients with contraindications to beta blockers or in angina patients in combination with beta blockers if the patients remain symptomatic or have a heart rate  $>60$  b.p.m.

### Implementation of clinical trial results with ivabradine in clinical practice

I have used ivabradine in various clinical situations for patients with CAD: patients who could not be

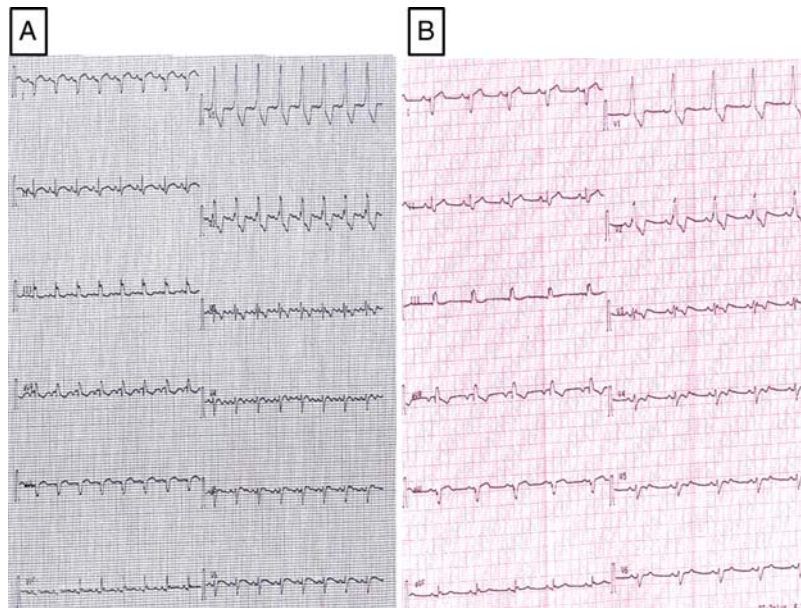


Figure 2 Patient ECG.

revascularized for one reason or another and patients who remain symptomatic or have a positive exercise tolerance test after successful revascularization. In these patients, ivabradine has been used with or without beta blockers. In this issue I present some clinical cases involving the use of ivabradine.

The first case regards a 72-year-old male with a history of hypertension, dyslipidemia, hypertension, and type 2 diabetes who was recently admitted to the hospital with unstable angina. The baseline ECG showed non-specific ST-T abnormalities and HR 90 b.p.m. He underwent coronary angiography which identified diffuse involvement of the three main coronary arteries, considered unsuitable for angioplasty or CABG. Optimized medical treatment was given, including nitrates, beta blockers (bisoprolol), calcium channel antagonists, ACE inhibitors, simvastatin, clopidogrel, and aspirin. The dose of bisoprolol was uptitrated to 10 mg od and the HR came down to 70 b.p.m. After 1 month the patient was still experiencing mild-to-moderate angina (class II–III). He was then put on ivabradine, uptitrated to 7.5 mg bid. After 2 weeks of treatment the HR came down to 60 b.p.m. and the patient became angina free.

The second case is a 55-year-old male with severe aortic stenosis, angina, and a history (20 years before) of lung tumor resection, followed by radiotherapy. He was also diagnosed with COPD and was being treated. ECG showed criteria for LVH and HR 100 b.p.m. Coronary angiography preoperatively also demonstrated significant proximal lesions in the right coronary artery. The patient underwent aortic valve replacement, but due to the presence of porcelain aorta it was decided to do a hybrid procedure with implantation of two stents in the right coronary artery. The patient was put on the usual antiplatelet and anti-ischaemic treatment, except for beta blockers, which were contraindicated in this patient.

After 1 month the patient was still experiencing mild chest discomfort and palpitations with regular exercise. This was attributed to small vessel disease and ivabradine was initiated and uptitrated to 7.5 mg bid. After 1 month the patient had an HR of 70 b.p.m. and was symptom free.

The final case regards a 28-year-old male who presented in the emergency room with acute ischaemia of the right lower limb secondary to arterial embolization caused by an LV apical thrombus. There was also distal septal and apical hypokinesia consistent with involvement of the LAD territory. The initial ECG (*Figure 2A*) showed sinus tachycardia with right axis deviation and right bundle branch block. The patient underwent coronary and peripheral revascularization and was anticoagulated. The work-up showed an anti-thrombin III deficiency. The patient was put on conventional medical treatment but could not tolerate beta blockers, so ivabradine was started because of persistent sinus tachycardia. At 5 mg bid the heart rate went down to 60 b.p.m. (*Figure 2B*), with no worsening of the baseline conduction abnormality.

These are some examples of patients with different patterns of coronary artery disease who showed a significant clinical benefit with ivabradine on top of anti-ischaemic treatment, either with or without beta blocker. These examples highlight the reasoning behind using ivabradine as an anti-ischaemic agent in different clinical situations where optimized anti-ischaemic treatment is not enough or when the use of beta blockers is contraindicated. Therefore, ivabradine represents an important addition to the current options of different anti-ischaemic agents that are available, with an impact on symptom relief and patient outcome.

**Conflict of interest:** none declared.



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