Ivabradine – The first If inhibitor for the treatment of chronic stable angina

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Abstract
Coronary artery disease (CAD) is a highly prevalent condition with life-threatening consequences. The most common presenting symptom of CAD is the chest pain associated with angina. Angina occurs when myocardial perfusion is inadequate to meet oxygen demand. An increased heart rate (HR) plays a vital role in CAD, not only as a trigger of most ischaemic events, but also as an important predictor of cardiovascular morbidity and mortality. Therefore HR reduction plays a central role in the management of patients with angina pectoris.

Current pharmacological management recommended by guidelines for the treatment of chronic stable angina includes β-blockers, calcium-channel blockers and organic nitrates. However, their use has limitations due to tolerance to the therapeutic effect, relative contraindications or side effects. In view of these limitations, a new pharmacological target was sought. This led to the launch of ivabradine, a selective and specific If inhibitor, which acts on the ionic currents for the regulation of pacemaker activity in the sinoatrial (SA) node cells. Ivabradine slows the slope of diastolic depolarisation of the action potential in the SA node cells and decreases HR at rest and during exercise.

Several clinical trials demonstrated dose-dependent anti-ischaemic and anti-anginal effects of ivabradine. There was no pharmacological tolerance or rebound phenomena upon withdrawal of ivabradine. Ivabradine was also found to have a good safety and tolerability profile with the main side effect being dose-related visual symptoms that were transient and mild in nature. Bradycardia may however be a problem with combination therapy.

Ivabradine is expected to give symptomatic relief to patients with chronic stable angina, especially those who have contra-indications or intolerance to current pharmacological options or who are insufficiently controlled on monotherapy. Long-term cardiovascular mortality benefits however need to be established.

Introduction
Angina is a symptom of atherosclerotic coronary artery obstruction, and occurs when myocardial perfusion is insufficient to meet myocardial oxygen demand.1,2 The results of the Framingham Heart Study showed that the lifetime risk of coronary heart disease for patients aged 40 years is 31% for females and 48% for males.3 In addition, several large-scale epidemiological studies such as the Chicago epidemiological studies and the National Health and Nutrition Examination Survey (NHANES) support elevated resting HR as a risk marker for both cardiovascular and all-cause mortalities.4,5 Since HR is the most important determinant of myocardial oxygen use, it is understandable that an increase in HR is accountable for the majority of cardiovascular episodes in CAD patients.5 An increased HR induces myocardial ischaemia and subsequent angina due to an increase in myocardial oxygen demand and decrease in myocardial perfusion, the latter as a result of shorter diastole duration.2,6

A lower HR is associated with a better prognosis for patients with CAD and has beneficial effects for the prevention of angina.7,8 Therefore, HR reduction is an important tool in the management of stable angina. A decrease in HR increases the diastole duration relative to cardiac cycle length, thereby allowing more time for effective coronary perfusion and left ventricular filling.1,5 Furthermore, theoretically, the lowering of HR may also be advantageous in the prevention of myocardial infarction, as the haemodynamic stresses placed on the myocardium by a high HR are associated with coronary plaque rupture.1,6,8

Ivabradine is a novel, selective and specific inhibitor of the cardiac pacemaker If current in the SA node. It inhibits the If current in a dose-dependant manner, thereby decreasing both HR and myocardial oxygen demand at rest and during exercise.1,2,8 Ivabradine was launched in South Africa in January 2009 by Servier Laboratories under the trade name Coralan® and is indicated for the symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm who have a contra-indication or intolerance to β blockers.8,10,11

Role of the If current
The myocytes of the SA node are the primary pacemaker cells of the heart and therefore control HR.1,4,8,12,13 The
pacemaker function involves several ionic currents that influence spontaneous diastolic depolarisation of the SA node. One of the most important of these is the If current.\textsuperscript{2,5} This current has atypical or “funny” properties compared to other current systems, such as mixed Na+-K+ inward movement, activated on hyperpolarisation and intracellular cyclic adenosine monophosphate (cAMP), low single-channel conductance and slow kinetics.\textsuperscript{1,8,12}

The If current is modulated by the autonomic nervous system. A rise in intracellular cAMP under the influence of β-receptor stimulation results in an increase in the If current and the diastolic depolarisation slope, which then leads to a decrease in the duration of diastole, producing an increase in HR. The opposite occurs when the muscarinic receptors are stimulated: diastolic duration increases resulting in a decrease in HR.\textsuperscript{1,4,8,13,14}

The function of the If current is to determine the slope of the diastolic depolarisation curve towards the threshold level which, consequently controls the time interval between successive action potentials, thereby playing a vital role in the pacemaking process.\textsuperscript{4,5,14} Refer to Figure 1.

The f channels responsible for the If current are part of the hyperpolarised-activated, cyclic-nucleotide-gated (HCN) channel family of which four distinct isoforms are found. These isoforms vary in terms of their properties and distribution in the different tissues such as the retina, brain and heart.\textsuperscript{4,12,13} The HCN4 channel is the isoform found in the heart and is active in the SA node. HCN4 channels found in the Purkinje fibers and the atrioventricular node are inactive under normal physiological conditions, but may operate under pathological conditions such as heart failure.\textsuperscript{4}

**Mechanism of action**

Inhibition of the If current is a valuable pharmacological target of reducing HR and providing a new approach to the treatment of ischaemic heart disease.\textsuperscript{4,8,14}

Ivabradine slows the HR by specifically binding to the If channels on the intracellular side of the plasma membrane of the SA node pacemaker cells and thereby selectively inhibiting the If current. The direct electrophysiological result of this inhibition is a decrease in the slope of the diastolic depolarisation in the SA node cells. This culminates in an increased time interval between consecutive action potentials and a decrease in HR both at rest and during exercise in animals and humans.\textsuperscript{4,5,8,14} Refer to Figure 2.

Ivabradine inhibits the If channel in the open phase when channels deactivate upon depolarisation and is relieved during hyperpolarisation in the closing phase, thereby acting as an open channel blocker.\textsuperscript{4,13,14,15} The inhibition is dose-dependent and appears to be current-dependent, suggesting that ivabradine is more active at increased heart rates.\textsuperscript{4,5,15}

β-blockers, unlike ivabradine, reduce If activation by decreasing sympathetic activity and cAMP formation, resulting in a lower HR. However, despite contributing directly to the decrease in myocardial oxygen use, the negative inotropic effects of β-blockers also limit the increases in coronary flow associated with HR lowering.\textsuperscript{1,4,5} Conversely, If inhibition with ivabradine does not alter myocardial inotropy or coronary vasomotor function, thus supporting cardiac output and coronary flow even during exercise.\textsuperscript{1,4,5,8} Left ventricular function and ventricular remodeling may however be improved with If inhibition.\textsuperscript{1,16}

**Current pharmacologic options**

The main goals in the treatment of patients with chronic stable angina are improving prognosis by preventing myocardial infarction and/or death and improving the functional status and quality of life by relieving the symptoms of angina.\textsuperscript{1,2,5,6,10} Conventional pharmacologic options to reduce symptoms are β-blockers, calcium-channel antagonists and organic nitrates.\textsuperscript{8,10,16,17} However, the use of these anti-anginal agents is limited by their frequent and sometimes severe side effects:\textsuperscript{2,8,16,17}

- β-blocker side effects include fatigue, depression, cold extremities, symptomatic bradycardia, sexual dysfunction and worsening of respiratory symptoms in asthma and chronic obstructive pulmonary disease.\textsuperscript{1,2,8,10}

![Figure 1: Action potential of the SA node cells](image1)

In phase 4 of the action potential, there is a slow, gradual depolarisation until threshold is reached (-50mV), and marked depolarisation occurs (refer to blue arrow). This spontaneous membrane depolarisation is accounted for by the If current. The orange highlighted area of the graph shows when the If current is activated.\textsuperscript{1,14}

(Adapted from César LAM. If Current and Heart Rate Control. Arq Bras Cardiol. 2007;88(4):e96-9)

![Figure 2: Effect of ivabradine on the action potential curve](image2)

AP = Action Potential

(Adapted from César LAM. If Current and Heart Rate Control. Arq Bras Cardiol. 2007;88(4):e96-9)
• Calcium-channel blockers may cause peripheral oedema, hypotension, constipation, headache and flushing.1,8,10
• Long-acting nitrates may cause light-headedness or headaches. Prolonged use of nitrates can also result in tolerance to the therapeutic effects and possible rebound vasoconstriction and angina when discontinued.1,10,17

Although not life-threatening, some mild side effects are common causes for poor treatment compliance with the anti-anginal medicines.16 The frequency of use of “combination therapy” to prevent or control angina symptoms also adds to the side effect burden. Adverse effects such as leg oedema, negative inotropy and hypotension frequently account for poor compliance, which in turn may exacerbate heart failure in patients with associated impaired ventricular function.8,16 These adverse effects associated with current anti-anginal treatment together with poor symptom control results in a persistent reduction in quality of life.16,17 In view of these side effects, a new pharmacological target was sought as a mechanism of lowering HR.1,8

Clinical trials of ivabradine
There have been several randomised clinical trials with ivabradine, comparing it either with placebo or active anti-anginal agents.

Efficacy and safety study
The clinical efficacy and safety of ivabradine were evaluated by Borer et al. Characteristics of the study are outlined in Table 1.

In this study, the following results were observed:16
• During the 2-week double-blind, dose-ranging phase, resting HR at trough of drug activity decreased relative to placebo in all three active treatment groups (p = 0.05). The clinical efficacy and safety of ivabradine were evaluated by Borer et al. Characteristics of the study are outlined in Table 1.

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In this study, the following results were observed:16
• During the 2-week double-blind, dose-ranging phase, resting HR at trough of drug activity decreased relative to placebo in all three active treatment groups (p = 0.05).
• Times to limiting angina and to angina onset nominally increased in all active treatment groups but reached statistical significance only in the 10mg bd ivabradine group. The intention-to-treat population group had similar changes, except that the decrease in time to limiting angina did not reach statistical significance (p = 0.058).
• Ivabradine-treated patients showed significant dose-dependent (p = 0.002) increase in total work performed at exercise tolerance tests (p = 0.019). There was significant superiority of 10mg bd ivabradine versus placebo for total work performed.
• Angina attacks and consumption of short-acting nitrates was decreased by ivabradine during the double-blind dose-ranging phase, although these changes did not reach statistical significance.
• There was no pharmacological tolerance or rebound phenomena on withdrawal of ivabradine.
• The incidence of adverse effects in all treatment groups was low and generally similar to placebo. However, visual symptoms were noted more frequently in the ivabradine group, i.e. by 1 patient each in the 2.5mg and 5mg groups and by 13 patients (14.8%) in the 10mg group, as opposed to no patients in the placebo group.

Ivabradine vs ß-blockers
The results of the International Trial of the Anti-anginal effects of IVabradinE compared to atenolol (INITIATIVE) as described in Table 2, showed that ivabradine demonstrated comparable efficacy to atenolol for both improving exercise capacity and for increasing time to exercise-induced ischaemia. For both drugs this improvement in exercise test parameters was associated with a two-third decrease in the number of angina attacks and short-acting nitrate use.2,6,19 The increase in exercise capacity per heart beat reduction with ivabradine could be attributed to the absence of vasoconstrictor or negative inotropic effects in the coronary arteries.5

The safety of atenolol vs ivabradine was not compared because two-thirds of the patients had previously used ß-blockers and were found to tolerate it. Furthermore, patients with known contra-indications or intolerance to atenolol were specifically excluded from the study.2

Ivabradine vs a calcium-channel blocker
The study in Table 3 concluded that in patients with stable angina, ivabradine has comparable efficacy to amlopidine in improving exercise tolerance as well as increasing time to angina onset and time to limiting angina.16,20 Time to 1mm ST segment depression, a definition of cardiac ischaemia during a positive exercise ECG test, was similar between the two drugs.16,20,22

### Table 1: Description of the study by Borer et al.8

<table>
<thead>
<tr>
<th>Objective</th>
<th>To evaluate the anti-anginal and anti-ischaemic effects of ivabradine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>Randomised, double-blind, placebo-controlled trial</td>
</tr>
<tr>
<td>Study Population</td>
<td>360 patients with stable angina and documented CAD</td>
</tr>
<tr>
<td>Treatment</td>
<td>Ivabradine (2.5, 5, 10mg bd) OR placebo for 2 weeks, followed by an open-label 2 to 3 month extension on ivabradine (10mg bd) and 1 week randomised withdrawal to ivabradine (10mg bd) or placebo</td>
</tr>
</tbody>
</table>

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### Table 2: Description of the INITIATIVE study

<table>
<thead>
<tr>
<th>Objective</th>
<th>To compare the anti-anginal and anti-ischaemic effects of ivabradine and the ß-blocker atenolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>Randomised, double-blind, parallel-group non-inferiority trial</td>
</tr>
<tr>
<td>Study Population</td>
<td>939 patients ≥ 18 years with history of stable effort angina for ≥ 3 months, evidence of CAD, 2 positive ETT prior to randomisation</td>
</tr>
<tr>
<td>Treatment</td>
<td>4 weeks of ivabradine 5 mg bd or 50mg atenolol daily and 12 additional weeks of 7.5mg or 10mg ivabradine bd or 100mg atenolol daily</td>
</tr>
</tbody>
</table>

ETT = Exercise Tolerance Test
Both groups of ivabradine were also shown to be non inferior to amlodipine (p < 0.001) in preventing angina attacks and limiting nitrate use. It was however found that ivabradine had a superior effect on the reduction of rate-pressure product, which is a surrogate marker of myocardial oxygen consumption. Ivabradine had a similar safety compared to amlodipine.16,20

**Ivabradine in combination with current anti-anginal treatment**

Conventional anti-angina therapies often do not completely prevent symptoms – about 20% of patients do not respond adequately to b-blocker treatment alone.8 Adding a second agent is therefore the logical next step in order to achieve better control.10,16 There is evidence that combination therapy is more effective than monotherapy.5,10

In this regard, ivabradine has been tested in addition to conventional treatment in a number of studies, also with the hope to improve long-term cardiovascular outcomes.1,6,23,24

**ASSOCIATE study**

The efficacy and safety of combination treatment involving ivabradine was established in this study, as summarised in Table 4.

The ASSOCIATE study results showed that despite a standard dose of b-blocker, the addition of ivabradine in patients with stable angina pectoris significantly improves all parameters of exercise capacity. The combination of atenolol and ivabradine was also well tolerated. There was only a 1.1% withdrawal of patients due to sinus bradycardia in the ivabradine group compared to none in the placebo group. 1.8% of participants in the ivabradine group reported visual symptoms as a side effect versus 0.9% in the placebo group.23

**BEAUTIFUL study**

Previously, it was postulated that reducing HR could decrease cardiovascular events and mortality in patients with cardiovascular diseases, but due to confounding effects of standard treatment such as b-blockers and non-dihydropyridine calcium-channel blockers, this hypothesis could not be tested before. The BEAUTIFUL study (mortality-mortality EvAluAton of the I inhibitor ivabradine in patients with coronary disease and left-ventricular dysfunction) was therefore designed with this outcome in mind.24 Refer to Table 5 for characteristics of this study.

The results of the BEAUTIFUL study showed that ivabradine did not affect the primary endpoint and the results were similar in all sub-groups. The reason for a lack of benefit of ivabradine on the clinical endpoint could be attributed to the low HR at baseline, or to an insufficient decrease in HR.24

However, in patients with HR ≥ 70 bpm, ivabradine did decrease the incidence of endpoints related to CAD, such as admission to hospital for fatal and non-fatal myocardial infarction (p = 0.001, relative reduction of 36%). Coronary revasularisation was also reduced in this subgroup by 30% (p = 0.016). These observations are in line with reports that HR ≥ 75 bpm is detrimental.24

One reason for the lack of effect of ivabradine on the heart failure outcomes could be that the required HR reduction might differ according to the underlying disease. Possibly,

### Table 3: Description of ivabradine vs amlodipine study

<table>
<thead>
<tr>
<th>Objective</th>
<th>To compare the anti-anginal and anti-ischaemic effects of ivabradine to those of the calcium-channel blocker amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>Randomised, double-blind, non-inferiority study</td>
</tr>
<tr>
<td>Study Population</td>
<td>1195 patients with a ≥3 month history of chronic, stable effort-induced angina</td>
</tr>
<tr>
<td>Treatment</td>
<td>Ivabradine 7.5mg or 10mg bd or amlodipine 10mg once daily for 3 months</td>
</tr>
</tbody>
</table>

### Table 4: Description of the ASSOCIATE study

<table>
<thead>
<tr>
<th>Objective</th>
<th>To determine whether ivabradine could offer further anti-ischaemic and anti-anginal benefits in patients with positive exercise tests and using standard doses of b-blocker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>Double blind, parallel-group, international trial</td>
</tr>
<tr>
<td>Study Population</td>
<td>889 patients with documented CAD and a history of stable angina already treated with atenolol 50mg</td>
</tr>
<tr>
<td>Treatment</td>
<td>In addition to the b-blocker, either ivabradine 5mg bd for 2 months titrated up to 7.5mg bd for another 2 months, or placebo for 4 months</td>
</tr>
</tbody>
</table>

### Table 5: Description of the BEAUTIFUL study

<table>
<thead>
<tr>
<th>Objective</th>
<th>To determine whether the HR lowering effect of ivabradine in combination with appropriate CV treatment would decrease CV morbidity and mortality in patients with CAD and left-ventricular systolic dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>Randomised, double-blind, placebo-controlled, parallel-group study</td>
</tr>
<tr>
<td>Study Population</td>
<td>10917 patients with CAD and left-ventricular ejection fraction &lt;40%</td>
</tr>
<tr>
<td>Treatment</td>
<td>5mg ivabradine increasing to target dose of 7.5mg bd OR placebo in addition to appropriate CV treatment</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>Composite of CV death, admission to hospital for acute MI and admission to hospital for new onset or worsening of heart failure during a mean follow up of 19 months</td>
</tr>
<tr>
<td>Sub-group Analysis of the Placebo Arm</td>
<td>To test the theory that increased resting HR at baseline is a marker for subsequent cardiovascular morbidity and mortality</td>
</tr>
</tbody>
</table>

CV = Cardiovascular; MI = Myocardial Infarction
HR should be decreased to lower levels when it is in physiological response to the disease (e.g. in heart failure), than when it directly affects the disease such as in angina or myocardial ischaemia.24

The authors of BEAUTIFUL concluded that ivabradine was well tolerated with few adverse effects. No obvious safety concerns were raised with the combination treatment of ivabradine and the β-blockers.24 However, there was an increased incidence of bradycardia in the ivabradine treatment group (13% vs 2% for placebo), although only 21% of those who withdrew for bradycardia in the ivabradine group were symptomatic. Bonny and colleagues estimated that this difference in bradycardia could be statistically significant and that the clinical significance of this should be determined.24,26

The sub-group analysis of results in the placebo cohort showed that for HR of 70 bpm or more there was a 53% increase in hospital admission for heart failure, 34% excess in risk for cardiovascular death, 46% increase in hospital admission for myocardial infarction (fatal and non-fatal) and a 38% increase in coronary revascularisation as compared to patients with HR < 70 bpm. The risk for cardiovascular death and admission to hospital for heart failure outcomes was directly proportional to increased HR above 70 bpm, whereas the relation was less evident for coronary outcomes.25

Safety and tolerability
Throughout its clinical development phase, ivabradine has demonstrated a good safety and tolerability profile.6 Ivabradine was found to have no respiratory or sexual side effects, with the main adverse effect being dose-related, phosphene-like visual symptoms that were transient and mild in nature. These symptoms comprised of enhanced brightness in restricted areas of the visual field and were frequently associated with abrupt changes in light intensity.1,6,11 The symptoms occurred in about 2–18% of patients treated with ivabradine, depending on the dose used, but were well tolerated, causing < 1% of patients to withdraw from treatment.1,6,8,11,18,27 These occasional episodes could be related to the action of ivabradine at the HCN channels present in the retina.1,2,6,8,12 The visual symptoms however resolved spontaneously during treatment or after withdrawal of treatment.6,11,18,21

Ivabradine does not modify myocardial contractility or haemodynamic parameters.1,5,11 The low incidence of bradycardia (less than 1% of patients during monotherapy) could be attributed to the use-dependence of ivabradine’s action.5 Bradycardia may however be more problematic with combination treatment.24,26

The efficacy of ivabradine is also not reduced in patients in whom other anti-anginal agents are contra-indicated or less well tolerated such as asthmatics, diabetics or the elderly.16 Also, there were no signs of tolerance development and rebound angina occurrence with the abrupt discontinuation of ivabradine.1,6,8,16,21

Advantages of ivabradine
In light of the results of the clinical trials discussed above and the selectivity and specificity of its mode of action, ivabradine has the following advantages in patients with angina:
- Proven anti-anginal and anti-ischaemic effects6,10,11,18
- Preservation of left ventricular relaxation6,24
- Exclusive HR reduction6,8
- No negative inotropic effects6,8,11
- Absence of coronary vasoconstriction6,8
- Maintenance of blood pressure6,8,24
- Absence of bronchospasm linked with β-blockers5,24
- No effect on intra-atrial, atrioventricular or intraventricular conduction times11,24

Limitations of ivabradine
Ivabradine is not recommended for use in patients with cardiac arrhythmias that interfere with sinus node function. It is also not recommended to use ivabradine with the calcium-channel blockers verapamil or diltiazem due to the risk of increasing bradycardia.11,28 The use of QT prolonging medicines (e.g. quinidine, sotalol, tricyclic anti-depressants, anti-psychotics, etc.) together with ivabradine should be avoided since HR reduction may exacerbate QT prolongation.11

Ivabradine is contraindicated in the following situations:
- Bradycardia i.e. resting HR < 60 bpm11,28
- Severe hypotension < 90/50 mmHg11,28
- Moderate to severe heart failure11,28
- Second and third degree heart block11,28
- Acute coronary syndrome or unstable angina pectoris11
- Concomitant use of St John’s Wort11
- Severe liver dysfunction11
- Cardiogenic shock11
- Combination with strong cytochrome P450 inhibitors, e.g. macrolide antibiotics, HIV protease inhibitors, azole antifungals, etc.11
- Pregnancy and lactation (ivabradine has teratogenic effects in animals)11

Place in therapy
β-blockers, and to some extent calcium-channel blockers, represent the cornerstone in management of stable angina.5,6,8,10,16,17 Patient compliance and physician use of these treatments, as well as that of nitrates, may however be limited by contra-indications, development of tolerance or common side effects.1,5,7,8,17

Conversely, β-blockers have a confirmed track record and therefore the risk of adverse effects with β-blockers should be put into context of their established benefits.10,19,29,30 Due to the advantages regarding precautions and side-effects, β-1 selective agents are preferred over non-selective β-blockers.10,29,30 Chronic obstructive pulmonary disease (COPD) and asthma are relative contraindications to β-blocker use and caution is advised, but some authors believe that β-blockers should not necessarily be withheld in patients with mild-to-moderate well-controlled asthma.30

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Nevertheless, some patients do develop wheezing and bronchospasm with β-blockers, which then requires dosage decrease or withdrawal of treatment. In view of the current data on the efficacy and safety of ivabradine, there appears to be an important clinical role for the drug in patients with chronic stable angina. In these patients, ivabradine markedly improves all exercise tolerance test parameters and significantly decreases the number of angina attacks. Internationally, ivabradine has been recognised as follows:

- **The European Society of Cardiology (ESC) guidelines** for the management of stable angina pectoris recommend the use of ivabradine as an alternative treatment in patients that cannot tolerate β-blockade. Other options include calcium-channel blockers, long-acting nitrates or a potassium-channel opener (not available in South Africa).

- **The Scottish Medicines Consortium (SMC)** has accepted ivabradine for restricted use within the NHS Scotland for patients who have contra-indications or intolerance to both β-blockers and rate-limiting calcium-channel blockers.

- **The Midlands Therapeutics Review and Advisory Committee (MTRAC)** has stated that ivabradine is suitable for restricted prescribing upon specialist advice according to the licensed indications, i.e., for patients who have a contra-indication to or intolerance of β-blockers.

Mortality benefits in CAD patients without previous myocardial infarction have not been clearly demonstrated with any of the conventional anti-anginal treatments. Mortality benefits have also not been documented for ivabradine and therefore the challenge remains to improve long-term cardiovascular outcomes.

Nevertheless, ivabradine is as an alternative agent in patients in whom current pharmacologic options are contra-indicated or have intolerable side effects.

**Conclusion**

HR reduction is a key factor for the optimal pharmacological management of chronic stable angina. The I, inhibitor ivabradine is the first in its class to decrease HR without affecting other cardiac parameters. Exclusive HR reduction with ivabradine has exhibited anti-ischaemic and anti-anginal efficacy comparable to that of atenolol and to amiodipine and is therefore a valuable therapeutic alternative or addition.

Current safety data show good tolerability with transient visual disturbances and bradycardia as the only possible concerns. Long-term studies are required to support the safety data. In addition, whether pure HR reduction translates into decreased mortality in patients with angina and other cardiovascular disease, still needs further investigation.

**References**

11. Servier Laboratories South Africa (Pty) Ltd. Coralan® Package Insert. 2008 December

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