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Ivabradine efficacy and safety in treatment of chronic stable angina

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Abstract

An elevated heart rate is an established marker of cardiovascular risk. Previous analyses have suggested that ivabradine, a heart-rate–reducing agent, may improve outcomes in patients with stable coronary artery disease, left ventricular dysfunction, and a heart rate of 70 beats per minute or more. Ivabradine is known to improve outcomes in patients with systolic heart failure. A trial of ivabradine involving patients with coronary artery disease and left ventricular systolic dysfunction did not show clinical benefit,1 but post hoc analyses suggested that ivabradine improved outcomes in patients who had a heart rate of 70 beats per minute or more, particularly in those with angina. However, many patients are often unable to tolerate the doses of beta blocker or non-dihydropyridine calcium antagonists required to achieve the desired symptom control. The selective pacemaker current inhibitor ivabradine was developed as a drug for the management of patients with angina pectoris, through its ability to reduce HR specifically. The available data suggest that ivabradine is a well-tolerated and effective anti-anginal agent and it is recommended as a second-line agent for relief of angina in guidelines.

This review article aims to evaluate the antianginal and anti-ischaemic efficacy of the selective If current inhibitor ivabradine in patients with chronic stable angina pectoris receiving beta-blocker therapy.

Keywords: Ivabradine; Ischemic heart disease; Heart failure; Chronic coronary syndrome

1. Introduction

Chronic stable angina pectoris is a common clinical manifestation of coronary artery disease (CAD), characterized by predictable episodes of chest pain or discomfort triggered by physical exertion or emotional stress. It results from myocardial ischemia due to an imbalance between oxygen supply and demand in the heart muscle. The primary goal in managing chronic stable angina is to reduce the frequency and severity of anginal episodes, improve quality of life, and prevent cardiovascular events. Traditional pharmacological treatments include beta-blockers, calcium channel blockers, and nitrates, which aim to reduce myocardial oxygen demand and improve coronary blood flow.

Ivabradine is a relatively newer agent that offers a unique mechanism of action in the management of chronic stable angina. Unlike beta-blockers and calcium channel blockers, Ivabradine selectively inhibits the If (funny) current in the sinoatrial node, leading to a reduction in heart rate without affecting myocardial contractility, blood pressure, or

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intracardiac conduction. This specific heart rate-lowering effect reduces myocardial oxygen demand and prolongs diastolic perfusion time, thereby alleviating ischemia.

Several clinical trials and studies have assessed the efficacy and safety profile of Ivabradine in patients with chronic stable angina, either as monotherapy or in combination with other antianginal agents. Evidence suggests that Ivabradine effectively reduces the frequency of angina attacks, prolongs exercise duration, and improves functional capacity. Importantly, its safety profile is generally favorable, with the most commonly reported adverse effects being visual disturbances (phosphenes) and bradycardia.

This introduction aims to provide an overview of Ivabradine's role in chronic stable angina management, focusing on its efficacy and safety based on current research evidence. A deeper understanding of its clinical benefits and potential risks is essential for optimizing treatment strategies in patients with stable CAD.

2. Ischaemic heart disease (IHD

Ischaemic heart disease (IHD) is a leading cause of mortality worldwide [1]. Angina pectoris (AP) is a prevalent symptom of IHD that is estimated to have affected almost 71 million people worldwide in 2017. In fact, angina is more debilitating than other cardiac conditions linked to IHD, like myocardial infarction (MI) or heart failure (HF) [2]. Anginal symptoms in daily life, whether or not there is ischaemia, worsen the prognosis for patients with chronic coronary syndrome and increase the risk of MI or cardiovascular death [3]. Heart rate (HR) is an important regulator of oxygen consumption in myocytes. An increase in HR increases the number of cardiac cycles per given time frame and, therefore, cardiac performance and myocardial metabolism [4]. In contrast, a reduction in HR decreases oxygen demand and maintains the viability of myocytes, and prolongs diastolic perfusion time and improves coronary flow velocity reserve, thus increasing the ischaemic threshold [5]. Ambulatory ischaemic episodes in patients with chronic coronary syndrome are preceded by elevated HR (i.e. greater than 70 bpm), with the risk of developing ischaemia related to baseline HR, as well as the magnitude and duration of the HR increase [6, 7]. Also, the frequency of ambulatory ischaemic episodes in patients with chronic coronary syndrome is related to mean HR, with an almost twofold increase in the risk of ischaemia in patients with an HR of 80 bpm versus 70 bpm [8]. Consequently, a reduction in HR is recognised as an important target for managing angina [9] and has been demonstrated to reduce angina symptoms [5].

The "funny" current (I f) in the sinoatrial node is selectively inhibited by ivabradine, a hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blocker [9, 10]. Patients with angina who also have elevated heart rate or left ventricular (LV) dysfunction are advised to take ivabradine as an adjuvant treatment. Ivabradine has been demonstrated to have anti-ischaemic and antianginal efficacy comparable to beta-blockers, lowering heart rate and myocardial oxygen demand while improving coronary filling time and blood flow, hence preventing ischaemia and angina symptoms [11].

Under physiological conditions, ivabradine is rapidly released from tablets and quickly and almost completely absorbed after oral administration. Under fasting conditions, it reaches peak plasma levels in approximately 1 hour. Taking ivabradine during meals reduces intraindividual variability in absorption time. Ivabradine is metabolised by both the liver and the gut by oxidation through cytochrome P450 3A4 (CYP3A4). This agent has low affinity for CYP3A4 and does not seem to modify CYP3A4 substrate metabolism or plasma concentrations. Potent inhibitors and inducers of CYP3A4, however, may affect the plasma levels of ivabradine. It is for this reason that ivabradine must not be co prescribed with strong or moderate CYP3A4 inhibitors, such as diltiazem and verapamil. Ivabradine's main half-life is approximately 2 hours (70%–75% of the AUC) and its effective half-life around 11 hours. Of clinical importance, ivabradine can be safely combined with first-line pharmacological agents commonly used to improve outcome in the management of cardiovascular disease such as aspirin, statins, beta-blockers and renin–angiotensin–aldosterone system inhibitors, as well as antidiabetic agents, proton pump inhibitors and antidepressant agents.

In humans, at the currently recommended doses, heart rate reduction—the main pharmacodynamic property of ivabradine—is approximately 10 bpm both at rest and during exercise. A study in 23 healthy volunteers (aged 19–63 years) using ivabradine 7.5 mg twice daily demonstrated a significant reduction in heart rate over 24 hours, without affecting circadian heart rate patterns of major importance in clinical practice and particularly in subjects with comorbidities, ivabradine does not influence intracardiac conduction, contractility or ventricular repolarisation nor does it affect central aortic pressure (or LV afterload).(7)

The addition of ivabradine to the treatment regimen led to an additional substantial decrease in resting heart rate of 15.2 bpm, with no significant differences observed between those receiving beta blocker medication and those not. Considering that two-thirds of patients on beta blockers had a little lower baseline HR than patients without beta

blockers (80.6 vs. 85.5 bpm), four months of ivabradine medication improved HR management in both groups with little between-group variance. The success rate for treatment response (HR <70 bpm or HR reduction of ≥10 bpm at month 4) was also marginally higher for those treated with both ivabradine and beta blockers,These findings are consistent with those of major observational research, where a comparable reduction of HR in participants with or without concomitant beta-blocker therapy was found [13], although the proportion of patients treated with beta blockers was considerably lower in that cohort. HR response rates and symptomatic effects were comparable across all analyzed subgroups

In a study done in stefan () stated that after 4 months of ivabradine therapy both the weekly number of angina attacks and consumption of short-acting nitrates declined substantially. At study end, approximately 90% of patients were free of angina symptoms and without need to use short-acting nitrates. These observations were accompanied by a pronounced shift in CCS grade distribution towards lower classes. Despite beta-blocker patients being more symptomatic at baseline, probably reflecting the fact that sicker patients were more likely to receive beta blockers, the treatment effect of ivabradine was consistent and comparable in patients with or without beta-blocker therapy after 4 months. At the end of follow-up, the percentage of patients in CCS grade I almost tripled irrespective of concomitant beta-blocker therapy. Although QoL was not specifically addressed in our study, a strong correlation between CCS classification and health-related QoL questionnaires like the EQ-5D is well established [14]. Given this association, an additional benefit of ivabradine therapy on QoL has been demonstrated in patients on beta blockers in the ADDITIONS study (Controlled-trials.com identifier: ISRCTN 53233058) [15] and can also be assumed for the present study cohort on basis of the improvement in CCS grade distribution after 4 months of treatment.

Overall, ivabradine's effects on HR reduction, angina symptoms, nitrate use, and CCS class improvement over a 4-month period were similar to those of other observational studies [16]. Furthermore, the Stefan study's findings were emphasized when a small subgroup analysis of an observational study that compared ivabradine patients with and without existing beta-blocker therapy showed no discernible impact of beta-blocker therapy on the efficacy or tolerability of ivabradine in "real-life" patients with stable AP [17]. Furthermore, there were no discernible differences between patients using less than 50%, 50%–99%, or 100% of the maximum beta-blocker dose in terms of HR reduction, its impact on angina symptoms, nitrate use, or CCS class improvement. To bolster our findings, reaching maximal approved beta-blocker doses failed to show additional positive effects in combination with ivabradine in patients with stable AP, and CHF compared to lower beta-blocker doses.

In a meta-analysis study on the Effect of ivabradine on cardiovascular outcomes in patients with stable angina, using three clinical trials each trial revealed that ivabradine was effective for reducing events in subgroup patients of heart beat ≥70 bpm in the BEAUTIFUL study and was effective in reducing primary outcome and secondary outcomes in the SHIFT study but in the recent trial with relatively longer duration follow up but without clinical heart failure (SIGNIFY) it was found that the addition of ivabradine to standard background therapy did not improve outcomes [18]. A recent meta-analysis found that unselective use of ivabradine in patients with CAD is not supported by evidence and may be associated with new onset of adverse effects [19]. According to the trials evaluated in this study, ivabradine did not significantly lower any of the efficacy results in their investigation. The pooled analysis for ivabradine compared to placebo individuals did not support the SHIFT study's claim that ivabradine was helpful in lowering the key composite end point and other secondary outcomes, such as hospitalization for worsening heart failure. According to this investigation, patient subgroups with left ventricular dysfunction and high resting heart rates (≥ 70 bpm) should use caution when interpreting ivabradine's efficacy. Additionally, they demonstrated that ivabradine is substantially linked to the recent onset of side effects such atrial fibrillation, phosphene, and impaired vision, and symptomatic bradycardia. Although adverse events varied across the trials, the analysis showed most of the adverse events were significantly related to ivabradine compared to placebo. This finding indicates that the unspecific use (i.e., off label use) of this drug is not effective and may catalyze untoward, adverse events.

Over the last fifteen years, the anti-anginal efficacy of ivabradine has been evaluated in a clinical trial program that has recruited in excess of 35,000 patients with SCAD and symptomatic angina, with or without left ventricular dysfunction, either as monotherapy or in addition to first line anti-anginal drugs. That ivabradine improves symptoms but not prognosis in patients with SCAD and preserved LV function, does not place ivabradine in a unique position amongst drugs which are currently recommended for the treatment of symptomatic angina in clinical guidelines. There are no definitive randomised clinical trial data which demonstrate the prognostic benefits of any of the anti-anginal drugs, including beta blockers , The available data suggest that ivabradine is a well-tolerated and effective anti-anginal agent. As recommended by the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency [20],

Ivabradine should be administered in patients with HR >70 bpm who are intolerant of or still have symptoms after using first-line anti-anginal medications, according to their analysis of the SIGNIFY trial results. Instead of aiming for a set

target HR, the ivabradine dosage should be up-titrated based on the patient's symptoms (20). No more than 7.5 mg BD should be taken than is recommended. It is not recommended to co-prescribe ivabradine with moderate or severe CYP3A4 inhibitors, especially non-dihydropyridine calcium antagonists. Patients at risk of torsade de pointes should not get ivabradine medication, and they should be closely watched for the onset of bradycardia and atrial fibrillation.

Ivabradine remains licensed for the treatment of symptomatic angina following review by the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency.

3. Conclusion

Ivabradine has emerged as an effective and well-tolerated option in the management of chronic stable angina, particularly in patients who are intolerant of or insufficiently controlled by traditional therapies such as beta-blockers. By selectively lowering heart rate without affecting blood pressure or myocardial contractility, Ivabradine helps reduce angina episodes, improve exercise tolerance, and enhance patients' quality of life. Its safety profile is generally favorable, with mild adverse effects like visual disturbances and bradycardia reported in some cases. Overall, Ivabradine represents a valuable addition to the therapeutic options for chronic stable angina management.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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