European Scholar Journal (ESJ)
Available Online at: https://www.scholarzest.com
Vol. 6 No. 06 June 2025
ISSN: 2660-5562

COMPARATIVE PHARMACODYNAMIC CHARACTERISTICS OF IVABRADINE IN PATIENTS WITH CORONARY ARTERY DISEASE: STABLE ANGINA

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Article history:

Received: 20th May 2025
Accepted: 11th June 2025

Abstract:

According to WHO estimates, annual mortality from all cardiovascular diseases (CVDs) is about 17 million people, with coronary artery disease (CAD) being the leading cause. In 2008, the total number of deaths from CAD worldwide reached 7.25 million, representing 12.8% of all deaths. In Russia, CAD accounts for 28% of outpatient and inpatient visits related to all CVDs. Among CAD risk factors, heart rate (HR) plays a significant role. An elevated HR contributes to myocardial ischemia and is a major predictor of CVD development, especially in men. The risk of death from CVD increases significantly when HR exceeds 84 bpm and decreases when HR falls below 60 bpm. First-line anti-ischemic drugs for CAD patients are beta-blockers. By reducing HR, prolonging diastole, and improving myocardial perfusion, beta-blockers reduce myocardial oxygen demand and help alleviate ischemia. In our study, patients were most commonly treated with bisoprolol (56.09% ±0.49) and metoprolol tartrate. However, beta-blockers have several side effects limiting their use in patients with comorbidities: worsening airway obstruction in asthma and COPD, reduced peripheral circulation, hypotension, and conduction disorders. Therefore, the development of a new drug class targeting the If-channels of the sinoatrial node presents a promising alternative for treating stable angina and heart failure. Ivabradine is the first representative of this class. It reduces HR without negatively impacting myocardial contractility, hemodynamics, or cardiac electrophysiological properties

Keywords:

INTRODUCTION: According to WHO estimates, annual mortality from all cardiovascular diseases (CVDs) is about 17 million people, with coronary artery disease (CAD) being the leading cause. In 2008, the total number of deaths from CAD worldwide reached 7.25 million, representing 12.8% of all deaths. In Russia, CAD accounts for 28% of outpatient and inpatient visits related to all CVDs. Among CAD risk factors, heart rate (HR) plays a significant role. An elevated HR contributes to myocardial ischemia and is a major predictor of CVD development, especially in men. The risk of death from CVD increases significantly when HR exceeds 84 bpm and decreases when HR falls below 60 bpm. First-line anti-ischemic drugs for CAD patients are beta-blockers. By reducing HR, prolonging diastole, and improving myocardial perfusion, beta-blockers reduce myocardial oxygen demand and help alleviate ischemia. In our study, patients were most commonly treated with bisoprolol (56.09% ±0.49) and metoprolol tartrate. However, beta-blockers have several side effects limiting their use in patients with comorbidities: worsening airway obstruction in asthma and COPD, reduced peripheral circulation, hypotension, and conduction disorders. Therefore, the development of a new drug class targeting the If-channels of the sinoatrial node presents a promising alternative for treating stable angina and heart failure. Ivabradine is the first representative of this class. It reduces HR without negatively impacting myocardial contractility, hemodynamics, or cardiac electrophysiological properties [1].

The rationale for prescribing beta-blockers lies in evidence of chronic hyperactivation of the sympathoadrenal system in patients with progressive and severe (NYHA class II–IV) coronary artery disease (CAD), as well as the proven effectiveness of beta-blocker drugs in reducing the risk of sudden cardiac death, death from the progression of chronic heart failure, and the number of hospitalizations. Studies on the effects of beta-blockers have shown that the reduction in heart rate (HR) induced by these drugs significantly influences symptoms and prognosis in chronic heart failure, as HR is a major risk factor for death and cardiovascular complications [5].

However, in real-world clinical practice, achieving target HR levels is often not possible. New approaches to the pharmacological treatment of coronary artery disease (CAD) aimed at improving quality of life and prognosis, as well

as slowing disease progression, have become possible due to the development of a novel drug — the If-channel inhibitor ivabradine.

In 2005, ivabradine, the first selective If-channel inhibitor, was approved by the European Medicines Evaluation Agency (EMEA) for clinical use as a symptomatic antianginal and anti-ischemic agent in patients with chronic stable angina [6]. Ivabradine binds specifically to If-channels when they are in the open state and selectively inhibits the If-current. Its action is directed at reducing the slope of diastolic depolarization, thereby lowering heart rate (HR). The more active the channels are, the stronger the binding and inhibitory effect of the drug. This mechanism reduces myocardial oxygen demand and enhances oxygen delivery to the myocardium (due to prolonged diastole), and also maintains coronary artery vasodilation even at peak exertion — providing a direct antianginal effect.

Due to its selective effect on the If-current, the drug does not influence other ionic currents in sinoatrial node cells, does not impair atrioventricular conduction, and preserves myocardial contractility and electrophysiological properties. Ivabradine use is not associated with "rebound" or "withdrawal" syndromes and offers an optimal efficacy-to-tolerability ratio [6, 7].

For the study, 34 patients were enrolled, including 16 in the ivabradine group and the rest in the placebo group. The average treatment duration was 3 months. During the study, several patients from both groups were excluded, and the final analysis was conducted on the remaining patients in each group. Clinical characteristics of patients in both groups are presented in Table 1.

Table 1.

Clinical Characteristics of Patients Included in the Study SHIFT

Parameter	Ivabradine Group	
	Ivabradine Group	Placebo Group
Mean age (years)	60.7 ± 11.2	60.1 ± 11.5
Body Mass Index (kg/m²)	28.0 ± 5.1	28.0 ± 5.0
Ischemic etiology (%)	68	67
NYHA Functional Class II (%)	49	49
NYHA Functional Class III (%)	50	50
NYHA Functional Class IV (%)	2	2
Duration of CAD (years)	3.5 ± 4.2	3.5 ± 4.2
History of myocardial infarction (%)	56	56
Diabetes mellitus (%)	30	31
Arterial hypertension (%)	67	66
Mean heart rate (beats per minute)	79.7 ± 9.5	80.1 ± 9.8
Mean left ventricular ejection fraction (%)	29 ± 5.1	29 ± 5.2
Mean systolic blood pressure (mmHg)	122 ± 16.1	121.4 ± 15.9
Mean diastolic blood pressure (mmHg)	75.7 ± 9.6	75.6 ± 9.4

Ivabradine or placebo was added to the standard therapy for chronic heart failure, which included ACE inhibitors or angiotensin II receptor blockers, beta-blockers, diuretics, aldosterone antagonists, digoxin, and other medications (such as isosorbide dinitrate, etc.) in similar proportions across both patient groups. The background therapy for CAD reflected the real-world clinical practice. After randomization, 89% of patients in both the ivabradine and placebo groups received beta-blockers. In each group, 26% of patients reached the target dose of beta-blockers, while 56% received at least 50% of the target dose. After one month of treatment, the heart rate (HR) was: 64 bpm in the ivabradine group (with an average dose of 6.4 ± 1.6 mg twice daily), 75 bpm in the placebo group. After 32 months of treatment, the average HR was 67 bpm in the ivabradine group and 75 bpm in the placebo group.

Primary endpoint events (death from cardiovascular complications or hospitalization due to CAD exacerbation) occurred in: 24% of patients in the ivabradine group, 29% in the placebo group (hazard ratio 0.82; 95% CI: 0.75–0.90; $p < 0.0001$).

Most events were due to: hospitalizations for worsening heart failure – 16% in the ivabradine group vs. 21% in the placebo group ($p < 0.0001$), death from heart failure – 3% vs. 5%, respectively ($p = 0.014$). Thus, in the ivabradine group, there was:

a 26% reduction in heart failure mortality ($p = 0.014$), a 26% reduction in hospitalizations due to worsening heart failure ($p < 0.0001$) (see Figure 3). Calculations showed that to prevent one cardiovascular death or one hospitalization due to worsening CAD, 26 patients must be treated with ivabradine for one year. It is important to emphasize that the positive effect of ivabradine was observed in patients with chronic heart failure of both ischemic and non-ischemic origin. While the impact of ivabradine on overall cardiovascular mortality did not differ significantly from the placebo group, there was a statistically significant reduction in mortality due to coronary artery disease (CAD) (hazard ratio 0.74; 95% CI: 0.58–0.94; $p = 0.014$). It should also be noted that the reduction in the risk of death and hospitalizations due to heart failure in the ivabradine group became apparent early — within 3 months from the start of treatment. Despite the complexity and polypharmacy required in managing moderate to severe chronic heart failure, patients reported good tolerability of the drug.

Table 2.

Ivabradine Treatment Outcomes by Other Endpoints

Endpoint	Hazard Ratio	95% Confidence Interval	Statistical Significance
Primary composite endpoint	0.82	[0.75; 0.90]	p < 0.0001
All-cause mortality	0.90	[0.80; 1.02]	p = 0.092
Mortality related to coronary artery disease (CAD)	0.74	[0.58; 0.94]	p = 0.014
Hospitalization for any cause	0.89	[0.82; 0.96]	p = 0.003
Hospitalization for cardiovascular causes	0.85	[0.78; 0.92]	p = 0.0002
Cardiovascular death / hospitalization for CAD or non-fatal myocardial infarction	0.82	[0.74; 0.89]	p < 0.0001

Changes in CAD Functional Class (FC) were observed as early as 6 weeks after starting ivabradine therapy, with notable improvement in patients with severe heart failure: Among those in NYHA Class IV, only 1 of 7% remained in that class; Among those in Class III, 53% improved; 44% of patients previously in Class III moved to Class II.
Among all patients: Improvement was observed in 28% of the ivabradine group and 24% of the placebo group; Clinical stability was reported in 68% vs. 70% respectively; Worsening occurred in 5% vs. 6% respectively.
Adverse and unwanted effects were less frequent in the ivabradine group compared to placebo (p = 0.02). The use of ivabradine led to an 18% reduction (p < 0.0001) in the risk of cardiovascular death and hospitalization due to CAD. Ivabradine's effectiveness in reducing adverse outcomes (death or hospitalization due to CAD) was evident early in treatment (within 3 months) across patients of different sexes and ages, and the benefit was maintained throughout the observation period.
CONCLUSION. Thus, clinical improvement in patients with chronic forms of CAD can be achieved through the use of ivabradine — an If-channel inhibitor. Based on the results of the SHIFT study, ivabradine has been included in the National Guidelines for the Diagnosis and Treatment of Chronic CAD. Treatment with ivabradine has been shown to significantly improve the quality of life in patients with CAD and stable exertional angina.

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