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Research Article

Systematic Review on the Effect of Ivabradine in Patients with Coronary Artery Disease Undergoing Echocardiogram with Strain

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Abstract

Introduction: Cardiovascular diseases are the main causes of death in the population. According to data from the World Health Organization of 2016, of the 20.8 million deaths from these diseases, 9.2 million occur due to atherosclerotic coronary disease. The Strain is a technique used by echocardiography that evaluates the measurement of the deformation that undergoes the myocardial wall, during the cardiac cycle, in the longitudinal and circumferential directions, by the apical projection and transverse axis of the left ventricle (LV), strain-rate being quantification of this deformation.

Objective: It was to analyze, through literary review, the main results with the use of strain echocardiography in relation to the attenuation of metabolic disorders in patients with CAD under the effect of Ivabradine hydrochloride.

Methods: Following the criteria of literary search with the use of the Mesh Terms that were cited in the item below on "Search strategies", a total of 102 papers that were submitted to the eligibility analysis were collated and, after that, were selected around 53 studies, following the rules of systematic review - PRISMA.

Conclusion: The risk/benefit ratio of Ivabradine remains positive for the authorized therapeutic indications, provided that recommendations are followed to decrease cardiac risk. The benefits of using Ivabradine for the treatment of chronic angina pectoris and heart failure continue to outweigh the risks provided that physician recommendations are followed. Other benefits were improvement of the quality of life and cognition of participants.

Keywords: *Coronary Artery Disease; Echocardiogram With Strain; Optimization of Technique; Ivabradine*

Introduction

Cardiovascular diseases are the leading causes of death in the population. According to data from the World Health Organization of 2016, of the 20.8 million deaths from these diseases, 9.2 million occur due to atherosclerotic coronary disease (ACD) [1].

ACD is the most common cause of mortality in developed countries [1,2]. Comparing Brazilian patients with stable ACD from 40 to 75 years per 1,000 inhabitants with those from European countries, Brazil (58.4%) is surpassed only by England (59.0%) and Spain (81.5%) [20,24]. This disease is the main cause of death in some South American countries, such as Argentina (12.0%), Bolivia (11.0%) and Ecuador (8.0%). In Brazil, it is responsible for a large number of deaths and health care expenditures [2] (Figure 1).

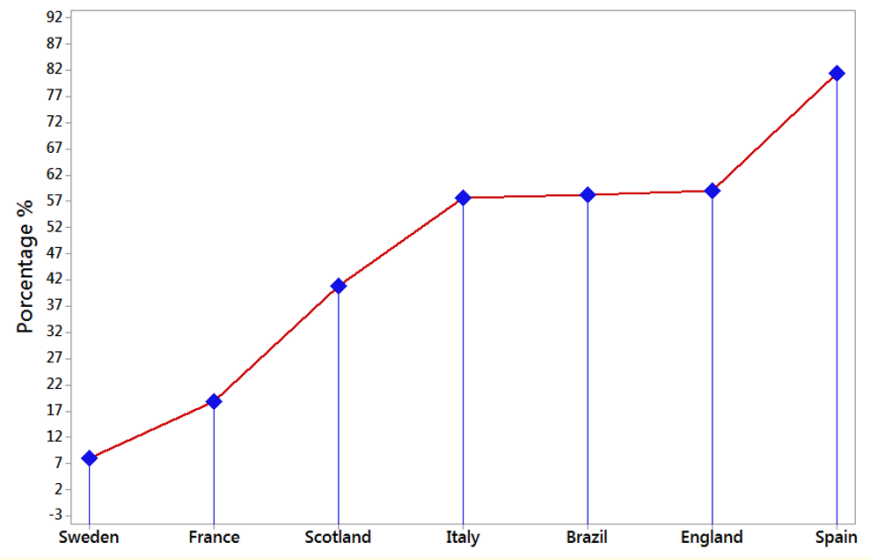

Figure 1: *Distribution of patients with stable coronary artery disease from 40 to 75 years old per 1,000 inhabitants.*

The typical clinical manifestation of chronic ACD is stable angina, characterized by pain or discomfort in the chest, epigastrium, mandible, shoulder, back, or upper limbs region. Usually, it is described by the patient as tightness, oppression, constriction or weight, being typically triggered or aggravated by physical activity or emotional stress and attenuated with rest and use of nitrates [3].

The pathophysiological manifestation of ACD involves coronary insufficiency, characterized by imbalance between supply and oxygen consumption at the myocyte level. Thus, the goal of treatment of stable angina depends on increased myocardial oxygen supply and reduced demand, which are closely related to contractility, left ventricular parietal stress, myocardial mass, and heart rate and post-load variations determined by blood pressure [4].

The diagnosis of ACD is based on the association of clinical history and complementary exams, since most patients with ACD present normal physical examination. Thus, a thorough history and evaluation of the personal and family history are fundamental. The exams are used for the investigation of ACD and follow-up of risk factors, being useful in the diagnostic definition and evaluation of its severity, including resting electrocardiogram, chest X-ray, simple ergometric test, echocardiography, myocardial scintigraphy, magnetic resonance imaging, coronary angiotomography and coronary angiography.

Strain is a technique used by echocardiography that evaluates the measurement of the deformation that undergoes the myocardial wall, during the cardiac cycle, in the longitudinal and circumferential directions, by the apical projection and transverse axis of the left ventricle (LV), strain-rate being quantification of this deformation [5]. The deformation of the myocardial wall is analyzed by the movement of selected points in the two-dimensional image of the myocardium, determining the speed with which they approach or move away from each other, throughout the cardiac cycle. The planes that measure the longitudinal and circumferential deformation are perpendicular to each other and the values of longitudinal deformations are presented as negative values, while a larger negative value indicates a greater degree of longitudinal deformation [5,6].

Objective of the Study

The objective of the present study was to analyze, through a literary review, the main results with the use of strain echocardiography in relation to the attenuation of metabolic disorders due to the imbalance between supply and demand of oxygen at the myocyte level, characteristic of ischemia even in the initial phase, and degree of deformation of the myocardial fibers in patients with ACD under the effect of Ivabradine hydrochloride. It was hypothesized from the clinical point of view that patients submitted to an echocardiogram with

strain after Ivabradine hydrochloride therapy would provide positive information, exposing the participant to minimal risks limited to the psychological character of the test, different from the inherent risks of other invasive tests.

Methods

Study design

Following the criteria of literary search with the use of the Mesh Terms that were cited in the item below on "Search strategies", a total of 102 papers that were submitted to the eligibility analysis were collated and, after that, were selected around 26 studies, following the rules of systematic review-PRISMA (Transparent reporting of systematic reviews and meta-analyzes-http://www.prisma-statement.org/).

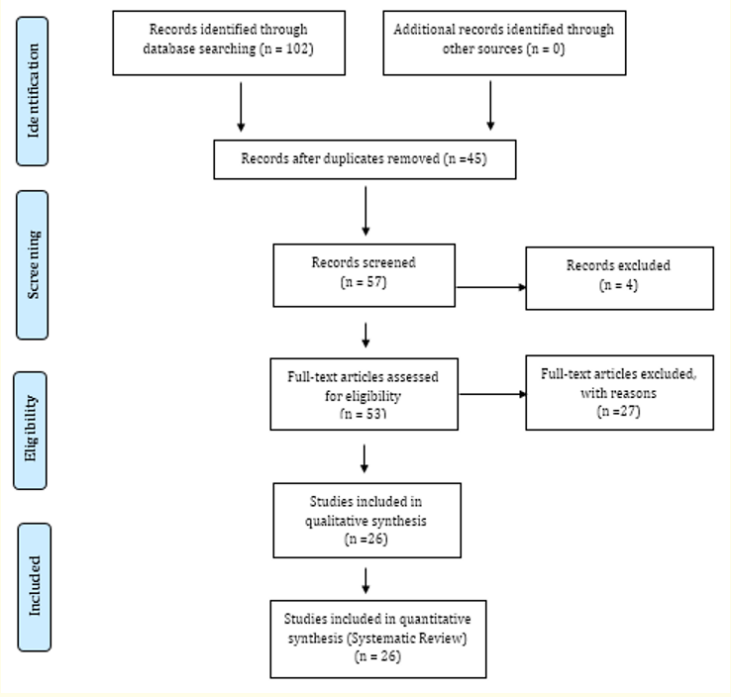

Figure: *Flow chart.*

Eligibility criteria and selection of studies

The inclusion criteria for participants in the studies that were evaluated in the present study included participants who presented an alteration of the Eco-Strain; Ivabradine or less than one (1) week of use, with 5.0 mg every 12 hours; participants who present pro-BNP; participants who have a heart rate equal to or greater than 60 beats per minute; anatomical diagnosis of coronary stenosis due to atherosclerotic disease previously identified by coronary angiography or coronary angiotomography; echocardiogram with previously altered strain; participants in treatment with standard therapy for atherosclerotic disease composed of at least classes such as platelet antiplatelet and statin.

On the other hand, those of exclusion were pregnant women and women in breastfeeding; occurrence of a new ischemic event during the course of the study or any invasive intervention such as angioplasty or revascularization surgeries; in cardiogenic shock (cardiac disease requiring hospitalization); AMI for less than 7 days; severe hepatic impairment; in the use of antimicrobial azolic derivatives; macrolides, antiretrovirals for treatment of HIV or nefazodone; cardiac arrhythmia such as atrial fibrillation or atrial flutter; advanced atrioventricular block and concomitant use of Ivabradine with verapamil or diltiazem.

Sources of information

The review protocol was based on the criteria of literary search with the use of mesh terms in the main databases such as Pubmed, Medline, Bireme, EBSCO, Scielo, etc. All references are registered in EndNote by the site: http://www.myendnoteweb.com/EndNoteWeb.html?cat=myrefs&.

Search strategy

In general, as an example, the search strategy in MEDLINE/Pubmed, Web Of Science, ScienceDirect Journals (Elsevier), Scopus (Elsevier), OneFile (Gale) followed the following steps: - search for mesh terms (Coronary artery disease; echocardiogram with strain, optimization of technique, Ivabradine, clinical trial), - use of the bouleanos "and" between mesh terms and "or" among historical findings.

Main outcomes

Primary outcome

Improvement through the use of Ivabradine hydrochloride for metabolic disorders due to imbalance between supply and demand of oxygen at the myocyte level (anti-ischemic action), characteristic of ischemia even in the initial phase, evidenced by the degree of myocardial fiber deformation, demonstrated by echocardiogram with strain.

Secondary outcome

Improvement of the quality of life and cognition.

Results and Discussion

The normality test was non-normal. After that, the Kruskal-Wallis nonparametric analysis reported that there was no statistically significant difference between each group of analysis (metabolic disorders, early phase ischemia and myocardial fiber deformation) with the group "Attenuation with Ivabradine", with $p > 0.05$ (Figure 2), that is, in fact the administration of Ivabradine considerably reduced the problems arising from ischemia after analysis with EcoStrain. Figures 3 and 4 show the percentage and propensity score of the events metabolic disorders, early stage ischemia and deformation of the myocardial fibers found in the 26 literary works, as well as the important response of Ivabradina in the attenuation of these ischemic events and the success of the analysis by EcoStrain.

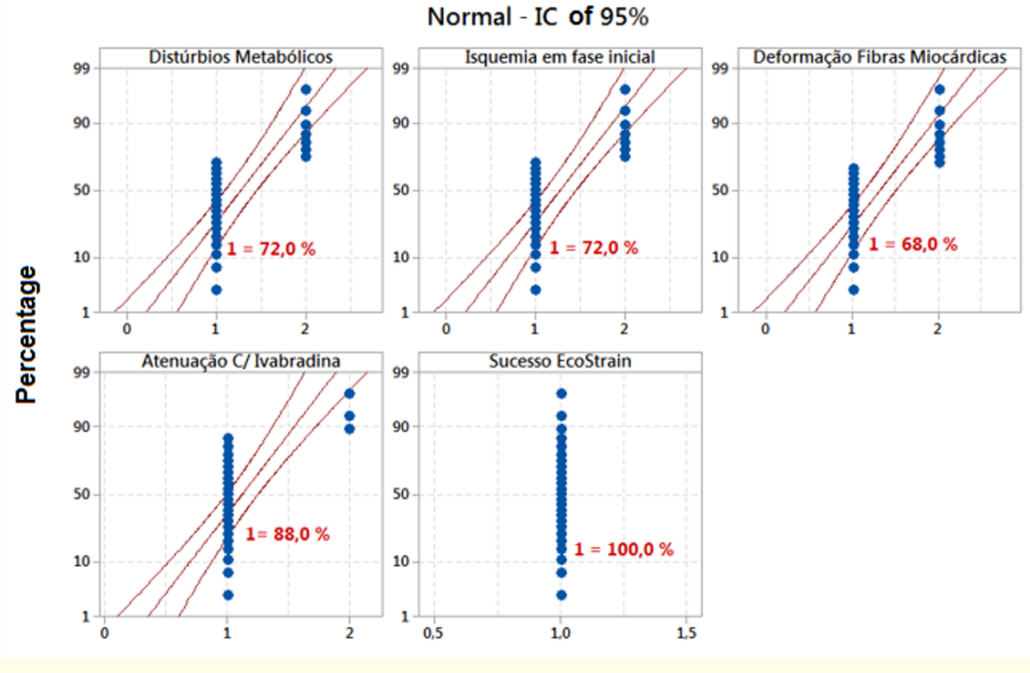

Figure 2: *Probability plot showing the values of score and percentage in relation to the events metabolic disorders, initial phase ischemia, myocardial fiber deformation, attenuation with Ivabradine and success EcoStrain.*

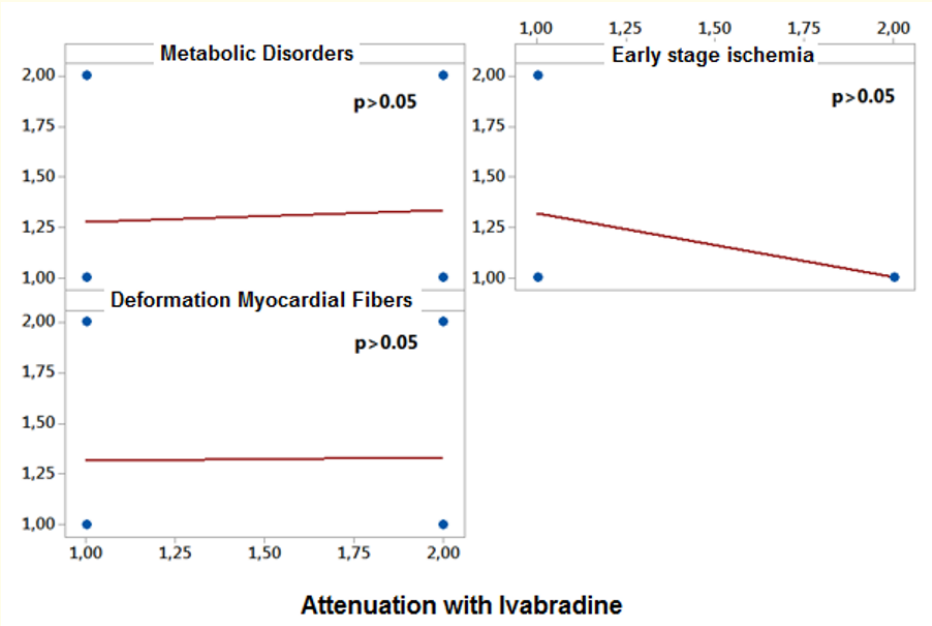

Figure 3: *Kruskal-Wallis non-parametric correlation graph showing p > 0.05 with statistical similarity between the events metabolic disorders, early phase ischemia, myocardial fiber deformation and attenuation with Ivabradine.*

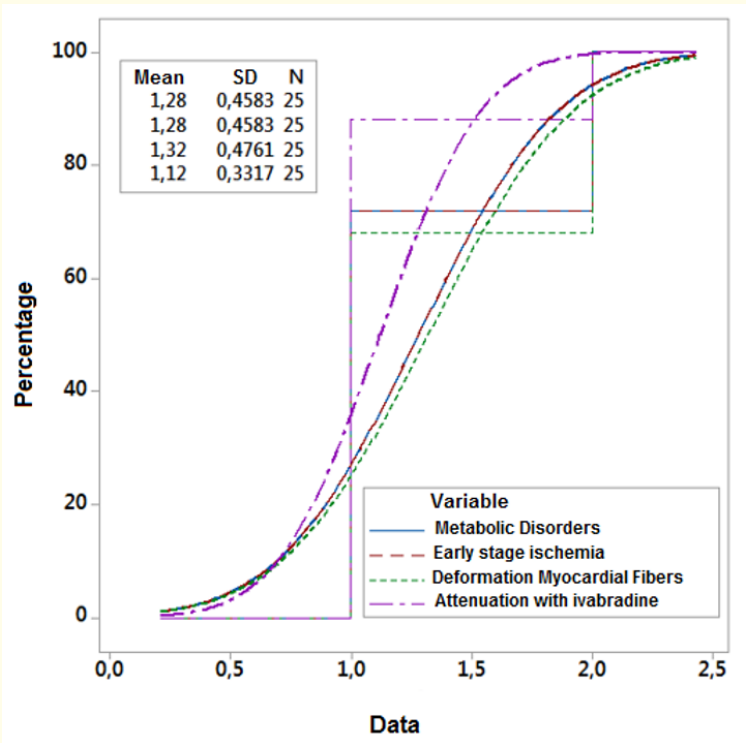

Figure 4: *Empirical FDA model chart showing propensity scores by means of mean values and standard deviation of the events metabolic disorders, early stage ischemia, myocardial fiber deformation and attenuation with Ivabradine.*

The studies on the effect of Ivabradine hydrochloride on participants with CAD submitted to echocardiography with strain were relevant, since this examination, besides being non-invasive, makes it possible to evaluate metabolic disorders due to the imbalance between supply and demand of oxygen at the myocyte level, characteristic of ischemia even in the initial phase, evidenced by the degree of deformation of the myocardial fibers visualized by means of images obtained by the echocardiogram with strain. In addition, the benefits of Ivabradine hydrochloride included improved symptomatology and quality of life, but data on the anti-ischemic action of the drug, detected by imaging methods, are scarce in the literature.

ACD is characterized by the presence of atherosclerotic plaques in the coronary vascular territory that determines insufficiency of blood supply to the heart (coronary insufficiency). There are several risk factors for CAD such as diabetes mellitus, systemic arterial hypertension (SAH), smoking, dyslipidemia, stress, sedentary lifestyle, among others [18,24].

The echocardiogram with strain allows the measurement of systolic and diastolic ventricular function, myocardial segmental function, detection of viability in hibernating walls, differentiation of athlete's hypertrophic cardiomyopathy, and measurement of contraction timing changes [5]. In addition, because it represents an examination with minimal risks to patients, it becomes an attractive non-invasive alternative. Reduced deformation despite preserved EF can be explained through geometric factors. Due to geometric confounders, strain better reflects systolic function in patients with preserved EF [7].

The deformation of the myocardial fibers is a marker of the onset of cardiac function disorders caused by diseases such as hypertension, diabetes and ischemia. The quantification of the LV longitudinal strain rate using strain echocardiography showed to be a sensitive method for the identification of ACD with hemodynamically significant lesions, transmural myocardial infarction as well as acute or subacute ischemia [5,22].

Therefore, two-dimensional SI detected dose-related regional myocardial dysfunction in the acute phase after RT in chemotherapy-naive left-sided breast cancer patients. Although the long-term effects remain unknown, this imaging modality may have a potential role in the evaluation of irradiation-related cardiotoxicity [9].

The systematic review work by Mangion., *et al.* [10], the prognostic value of longitudinal strain is less certain. Strain differentiates between infarcted versus non-infarcted myocardium, even in patients with stable ischemic heart disease with preserved left ventricular ejection fraction. Strain recovery is impaired in infarcted segments with intramyocardial hemorrhage or microvascular obstruction. There are practical limitations to measuring magnetic resonance cardiac resonance in the acute setting, and knowledge gaps, including the lack of data showing incremental value in clinical practice. Studies of cardiac magnetic resonance imaging in patients with ischemic heart disease have been limited by sample size and design. Strain imaging has potential as a tool for assessing early or subclinical changes in left ventricular ejection fraction function, and strain is now being included as a surrogate measure of outcome in therapeutic trials.

Left ventricular global longitudinal strain and left atrial volume index are independently associated with adverse outcome in patients with hypertrophic cardiomyopathy and may help to optimize risk stratification in these patients [11].

The evaluation of the segmental and global function, which is related to the left ventricular ejection fraction, has importance as a diagnostic and prognostic aid. However, it does not always reflect the true extent of myocardial injury, since the presence of compensatory hyperkinesia may result in almost normal ejection fraction, despite myocardial injury in the ischemic zone, affecting the real value studied [6]. Therefore, the analysis of myocardial deformation using strain echocardiography is essential for the study of ventricular function, since it allows the detection of regional contractility and relaxation changes even before they appear in conventional echocardiography, presenting the possibility of differentiating the myocardial segments with active and passive deformation of motion [5,14].

The treatment of ACD can be clinical/medical or surgical. In drug therapy, drugs such as platelet antiplatelets, lipid-lowering agents, beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are considered indispensable in the management of patients with CAD [17,19].

Drug treatment, which aims to reduce myocardial ischemia, has three antianginal drugs: nitrates, beta-blockers and calcium channel blockers [16]. Nitrates are capable of causing vasodilation in coronary and systemic territory, increasing the supply of coronary blood and reducing the myocardial demand for oxygen. Beta-blockers aid in relieving symptoms by competitively inhibiting sympathetic stimulation, reducing contractility and heart rate, which infers increased diastolic time and improves coronary flow. Calcium channel blockers block the influx of this ion into smooth muscle cells and myocytes, causing coronary and peripheral vasodilation, decreased atrioventricular conduction and contractility [16].

Ivabradine opens a new therapeutic class in the treatment of stable angina, having antianginal and anti-ischemic action, being specific and selective inhibitor of the current "If" of the sinoatrial node, modulating the influx of the ionic currents and determining, as a consequence, reduction heart rate, rest and exertion [15,21]. In addition to improving symptoms and quality of life, Ivabradine hydrochloride is associated with increased exercise capacity, reduced functional class, and improved cardiac performance in patients with heart failure.

In a recent study, the addition of Ivabradine to treatment with Beta-Blockers and replacement of Beta-Blockers resulted in a reduction in the heart rate (61 ± 6 vs. 63 ± 8 bpm; $p = 0.001$). At week 16, significantly more patients on Ivabradine + Beta-Blockers were on CCI class I than on Beta-Blockers (37.1% vs. 28%, $p = 0.017$) and significantly more patients were free of angina (50,6% vs. 34.2%, $p < 0.001$) [26]. The patient's health status based on the visual analogue scale was also better in the Ivabradine + Beta-Blockers group. Adverse events were significantly more common with Beta-Blockers titration than with Ivabradine + Beta-Blockers combination ($p < 0.001$). In patients with stable angina, combination therapy with Ivabradine + Beta-Blockers demonstrated good tolerability, safety and clinical improvement more pronounced, compared to titration Beta-Blockers [26].

According to Maranta., *et al.* [8], Ivabradine reduces both acute left ventricular ejection fraction dysfunction and stunning in patients with CAD and exercise-inducible ischaemia. We hypothesize that this mechanism might contribute to reduce chronic left ventricular ejection fraction dysfunction in patients with CAD. In this setting the drug might limit the development of hibernating myocardium which is believed to result from repeated episodes of ischaemia and stunning.

The meta-analyses suggests that Ivabradine is not effective in reducing cardiovascular-related morbidity and mortality unless used for specific conditions. However, the use of this drug was strongly associated with the onset of untoward and new adverse events. This finding strongly supports previous findings and further informs the rational and evidence-informed clinical use of Ivabradine [12].

The adverse effects of Ivabradine include bradycardia, atrial fibrillation and visual disturbances, but Ivabradine avoids the negative inotrope effects observed with β-adrenoceptor antagonists. In conclusion, in patients with EF < 35.0% and heart rate above 70 bpm, Ivabradine improves the outcome and might be a first choice of therapy, if beta-adrenoceptor antagonists are not tolerated. Further studies should show whether that can be extended to heart failure patients with preserved ejection fraction [13].

Conclusion

Studies on the effect of Ivabradine hydrochloride on participants with ACD submitted to echocardiogram with strain were relevant, since this examination, besides being non-invasive, makes it possible to evaluate metabolic disorders due to imbalance between supply and demand of oxygen. The risk/benefit ratio of Ivabradine remains positive for authorized therapeutic indications, provided that recommendations are followed to decrease cardiac risk. Ivabradine had no beneficial effects in cardiac patients without clinical heart failure. However, the benefits of using Ivabradine for the treatment of chronic angina pectoris and heart failure continue to outweigh the risks. Other benefits were improvement of the quality of life and cognition of participants.

Limitations

Data on the anti-ischemic action of the drug, detected by imaging methods, are scarce in the literature. In addition, Ivabradine had no beneficial effects in cardiac patients without clinical heart failure.

Declaration of Potential Conflict of Interest

The authors declare no conflict of interest.

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