J Cardiovasc Disease Res., 2020;11(1):04-08.
A Multifaceted Peer Reviewed Journal in the field of Cardiology
www.jcdronline.org | www.journalonweb.com/jcdr

Review Article

Review Article: Impact of Ivabradine on Cardiovascular Morbidity

Gammone MA[1]*, Riccioni G[2], D'Orazio N[1]

[1]*Department of Oral Medical and Biotechnological Sciences, Via dei Vestini 31, University of Chieti-Pescara, Italy*

[2]*Cardiology Unit, San Camillo de Lellis Hospital, Via Isonzo 1, Manfredonia, Foggia, Italy*

Correspondence
Gammone MA,
Department of Oral Medical and Biotechnological Sciences,
Via dei Vestini 31
University of Chieti-Pescara
Italy
E-mail address: m.alessandra.gammone@gmail.com

Submitted: 23-11-19
Revision: 20-12-19
Accepted date: 14-01-20

DOI: 10.5530/jcdr.2020.11.02

ABSTRACT

Heart failure is a complex clinical syndrome with a high incidence all over the world. Although various types of pharmacological and device therapies are available, the control of increased heart rate (HR) is critical. The bradycardic agent, ivabradine (IVA), has been displayed to reduce HR by inhibiting the funny current (If). The underlying mechanism states that ivabradine can enter the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels and bind to the intracellular side, subsequently inhibiting the If. This phenomenon can prolong the slow spontaneous phase in the diastolic depolarization, and thus, reduce HR. Many epidemiological studies reported a strong independent association between elevated heart rate and major cardiovascular risk factors including atherosclerosis, ventricular arrhythmias, and left ventricular dysfunction. The heart rate reduction with IVA is beneficial in patients with coronary artery disease CAD, chronic stable angina pectoris, and chronic heart failure (CHF), with acceptable tolerance and safety profile. The pharmacodynamic and pharmacokinetic properties of this drug make it an important agent in the management of patients with CAD and HF. The aim of this short review is to explore recent results with IVA a new medication that lowers heart rate by selectively inhibiting the *If* current, and to describe others future potential applications.

Key words: cardiovascular disease, chronic stable angina, chronic heart failure, heart rate, ivabradine.

INTRODUCTION

There is a close relationship linking elevated resting HR to cardiovascular morbidity and mortality[1] in normal individuals and in patients with coronary events and CHF[2] since a consistent HR reduction decreases myocardial oxygen demand and improves endocardial blood supply. In particular, in CHF the heart cannot pump blood efficiently and it is unable to meet the body's demands of oxygen, and there is an increased end-diastolic pressure, with a higher risk of readmission for hospital and mortality when HR is above 70 bpm[3] An increase in HR as a consequence of increased sympathetic activity may trigger ischemic events[4] because HR is a major determinant of myocardial oxygen consumption and energy utilization; furthermore, an increase in HR reduces the diastolic coronary perfusion time[5]. Therefore, its decrease would certainly be beneficial in patients with cardiovascular diseases: a lower resting HR would be of particular benefit in patients with ischemic heart disease and/or heart failure. During the past half-century, age-adjusted cardiovascular disease-related mortality has declined by about two-thirds in industrialized countries. CHF is a notable exception: despite important advances in therapy during the past two decades, hospitalization and mortality rates remain relatively high in these patients: in the USA, hospitalizations have risen steadily since 1980 up to one million discharges per year[6]. In Europe, 1–2% of the population suffer from CHF, with the prevalence rising to ≥ 10% among the population aged ≥ 70 years and a death rate about 30/100,000[7].

From a pathophysiological point of view, heart failure is divisible into two sub-classes, the first comprising patients with left ventricular systolic dysfunction, representing a sub-class of heart failure with reduced ejection fraction (HFrEF), and the second including patients with a "preserved" systolic function, which represent a sub-class of heart failure with preserved ejection fraction (HFpEF). Since betablockers became part of standard therapy for HFrEF, it was evident that cardiac rate slowing is an underlying basis of clinical effectiveness of HFrEF therapy. With the discovery of the "f current" that modulates the slope of spontaneous diastolic depolarization of the sino-atrial node, a non-betablockade approach to HR slowing became available. IVA, the first FDA-approved f-current blocker for HFrEF, markedly reduces hospitalizations for worsening heart failure, while also progressively reducing mortality as pre-therapy HR increases, and also promotes beneficial left ventricular remodeling, improves health-related quality of life and is effective despite a wide range of comorbidities[8]. The drug is well tolerated, and adverse effects are relatively few. IVA represents an important addition to the armamentarium for mitigation of HFrEF

Current treatments for CHFrEF include not only β-adrenoceptor antagonists, but also angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor type 1 (AT1) antagonists, aldosterone receptor antagonists, diuretics, digoxin and a combination drug with AT1-receptor antagonist and neprilysin inhibitor. Although β-blockers and non-dihydropyridine calcium channel-blockers are effective at lowering HR, they bring other pharmacologic effects that may not be desirable in some patients, such as negative inotropy. IVA is a drug specifically designed to lower HR without any other demonstrable pharmacologic effects: it is a pure heart rate-lowering drug. It functions by blocking the hyperpolarization-activated cyclic nucleotide gated channels (f-channels) specific for the sinoatrial node and disrupting *I*(f) ion current flow. This effectively prolongs diastolic depolarization and slows firing in the sinoatrial node, which lowers HR. Its effects are mainly pronounced at higher HR, which is important in minimizing the development of symptomatic bradycardia. Consequently, IVA is a novel unique drug, which may be of benefit with higher baseline HR, but detrimental with low baseline HR[9]. β-blockers are widely used also in chronic stable angina (CSA) and after myocardial infarction (MI). At least part of their activity involves HR lowering. However, these agents can have undesirable negative inotropic activity and can cause a paradoxical vasoconstriction of large epicardial coronary arteries at rest and during exercise[10]. Additionally, not β_1 selective β-blockers may cause bronchoconstriction in patients with chronic obstructive airway disease[11] and may have negative metabolic effects, including a reduction in insulin sensitivity. A selective HR-lowering agent that does not produce these undesirable effects could thus be of therapeutic value[12]. Previous researches suggest that IVA exhibits an acceptable and favorable benefit-risk profile, and this drug should be considered as a viable option in patients with CSA and CHF[13].

EFFECTS OF IVABRADINE

Chemistry and discovery of ivabradine

IVA is a water-soluble medication with a fast-intestinal absorption and high first-pass metabolism, which give it a bioavailability of about 40%. IVA has a half-life of approximately 11 hours[4].

After oral administration, it is metabolized by CYP3A4 in the intestines and the liver and peak plasmatic concentration are reached in about one hour. Less than 5% of its ingested dose is excreted in urine and a minimum part in feces, with IVA' s main metabolite being N-desmethylated[14].

Table 1. Overview of clinical trial.

Trial	Result
BEAUTIFUL study[24]	Reduction in hospitalization for CAD outcomes (in the subgroup with HR> 70 bpm)
SHIFT study[36,37]	Reduction in death and hospitalization for worsening HF
INITIATIVE study[29]	Augmented exercise capacity and prolongation of exercise test duration
ASSOCIATE study[28]	Augmented total exercise duration and improved secondary exercise test criteria
REDUCTION study[32]	Further HR reduction in patients remaining symptomatic despite treatment with β-blockers

The use of this drug has been approved by the European Medical Agency in 2005 for the treatment of stable angina, and by the Food and Drug Administration in 2015 to reduce hospitalization from worsening heart failure, but the first drug discovery programs date back to 1980s, when the specific bradycardic agents have been discovered and divided in three different groups (imidazolines, aminopyrimidines and phenylalkylamines) according to their chemical structure[15].

IVA specifically acts on HCN channels: it binds to the subfamily of hyperpolarization-activated HCN4-channels, which creates the *I*(f) current. It diffuses across the cellular membrane and binds intracellularly to the HCN4 channel when it is in its open state. The number of open channels directly correlates with the amount of depolarizations: this implicates the rate-dependent nature of ivabradine, where a higher HR makes the drug more effective. The depolarization of the SA node cells is prolonged by blocking the channel and thereby stopping the *I*(f) current, thus resulting in lowering of the HR[4].

Mechanism of action of ivabradine

IVA's primary mechanism of action on cardiac tissue is on the sinoatrial node, which occupies a predominantly subepicardial position at the junction of the superior vena cava and the right atrium. It blocks the intracellular aspect of the hyperpolarization-activated cyclic nucleotide–gated transmembrane channel, which is responsible for the transport of sodium and potassium across the cell membrane, in the open state: this results in inhibition of the inward funny current *I*(f), which is specifically activated at hyperpolarized membrane potentials. By selectively inhibiting *I*(f), there is a reduction in the slope of diastolic depolarization of the pacemaker action potential and an increase in the duration of diastole, without altering other phases of the action potential[16]. This results in HR reduction. For this reason, IVA is a specific HR-lowering agent, which has selective action on pacemaker activity in the sinoatrial node of the heart, resulting in important differences compared with non-selective HR reducing agents, such as β-blockers[12]. It decreases HR and myocardial oxygen consumption at rest and during exercise[17-19]. IVA is licensed for the treatment of CSA in patients with normal sinus rhythm, who have a contraindication or intolerance for β-blocker drugs, or in combination with betablockers in patients inadequately controlled with an optimal betablocker dose and whose HR is > 60 bpm[20]. IVA is the first of a new class of HR-reducing agents without other direct cardiovascular effects (negative inotropic effect, blood pressure reduction)[21,22]. It has an excellent tolerability and safety profile and can be safely combined with other currently used cardiovascular drugs, including β-blockers[23]. The HR-reducing effect of IVA is proportional to resting HR; extreme sinus bradycardia is uncommon.

Pharmacology and clinical trials of ivabradine

In the BEAUTIfUL (morBidity–mortality EvAlUaTion of the If inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction) study, symptomatic bradycardia was the most common adverse effect leading to discontinuation of treatment, even if it remained a rare event[24]. The QT interval is prolonged with the decreased HR, for this reason this specific HR-reducing drug should not be administered with agents with QT-prolonging effects. However, with appropriate correction for HR or, in studies of direct comparison of the QT interval, when the influence of the HR was controlled by atrial pacing, no significant effect of IVA was found on ventricular repolarization duration[25], QT duration, QT dispersion, or maximum and minimum QT duration[26,27]. IVA reduces HR by selective inhibition of the If current in the sinoatrial node with no declared direct effect on the autonomic nervous system (ANS). However, IVA's protective effects might also reside in the modulation of the ANS by affecting the intrinsic cardiac nervous system, so that it could be effective in the treatment of autonomic dysfunction-related diseases setting a new autonomic balance[28].

IVA (5.0, 7.5, and 10.0 mg bid) resulted to be as effective as atenolol (50 or 100 mg/day) in terms of antianginal and anti-ischemic efficacy in 939 patients with CSA in INITIATIVE (INternatIonal TrIAl on the Treatment of angina with IVabradinE versus atenolol)[29], where the augmented exercise capacity was associated with a prolongation of exercise test duration. Another study, ASSOCIATE (evaluation of the Antianginal efficacy and Safety of the aSsociation Of the I_f Current Inhibitor ivAbradine with a beTa-blockEr) explored the effect of IVA on top of atenolol 50 mg/day in 889 patients with CSA (28). In combination with atenolol, IVA induced a significant increase in total exercise duration (primary efficacy criterion) and improvement in other exercise test criteria (time to limiting angina, time to angina onset, and time to 1-mm ST-segment depression) compared with a placebo group receiving background therapy with atenolol. This study demonstrated that IVA can be added on top of β-blockers in CSA patients with insufficient HR reduction, in patients who remain symptomatic despite treatment with β-blockers[30], and in patients with refractory angina[31]. The results of IVA in the treatment of CSA in patients with CAD have been confirmed in everyday routine practice (REDUCTION Study)[32], independently of the severity of angina and the presence of comorbidities[33,34]. Further analysis in the 1507 patients in BEAUTIfUL who had angina at baseline demonstrated that IVA improved the primary outcome (the composite of cardiovascular death, MI and hospitalization for heart failure) by 24% and MI alone by 42%, relative to placebo[35].

The SHIfT (Systolic Heart Failure Treatment with the I(f) Inhibitor Ivabradine Trial) study was a randomized, double-blind study designed to compare IVA with placebo on outcomes in 6500 patients with symptomatic CHF (New York Heart Association [NYHA] class II-IV), left ventricular ejection fraction (LVEF) <35%, and a prior hospitalization for worsening heart failure within the previous 12 months. Randomized treatment (12-48 months) was given on top of guidelines-based therapy for CHF, including a β-blocker at optimized dose. Resting HR at baseline had to be >70 bpm[36]. The results of this study showed that IVA substantially and significantly improves outcomes in patients with CHF receiving the best possible evidence-based background treatment[37] and significantly reduced the cardiovascular death or hospitalization for worsening heart failure by 18% (P<0.0001).

Further applications: Ivabradine beyond heart failure

Treatment with IVA represents a new therapeutic alternative for patients with inappropriate sinus tachycardia[38-43], a syndrome characterized by a sinus heart rate higher than 100 bpm at rest with a mean daily HR higher than 90 bpm, which is associated with distressing symptoms of palpitations. Its mechanism is not precisely understood and is postulated to be multifactorial and complex. An enhanced sinus node activity and/or impaired sympathovagal balance seems to be the

long-term follow-up (82.1 ± 11.8 bpm after 4 years). Neither allograft rejection nor changes in left ventricular ejection fraction were observed over the follow-up period, without impairment of blood pressure, myocardial contractility and cardiac conduction.

Furthermore, experimental studies have identified the effects of HR on endothelial function: the endothelium plays a pivotal role in many biological processes, as modulation of vessel tone, of inflammatory and immunologic system and of platelets function[49,50]. However, the normal function of the endothelium is strictly connected to his health, anatomical and functional integrity. In this respect, an increased HR (or its reduced variability) have shown to be associated with coronary plaque's rupture and subclinical inflammation[51]. Blood vessels can adapt to increased mechanic wall stress and change their structure, getting benefits from HR reduction caused by IVA, with a final improvement of arterial elastance. Endothelial dysfunction is considered the ideal index to discover the first negative effects of the cardiovascular risk factors on the arterial system. In the traditional pharmacological therapy used in CHF, the only drug that demonstrated a positive action on the endothelium is nebivolol, but more recent data suggest that administration of IVA on top of optimized medical therapy may improve endothelial function[52-54].

The utilization of IVA in cardiogenic shock remains off label and has been considered a contraindication, because of the theoretical risk of attenuating compensatory tachycardia. Tachycardia, especially in the context of inotropic therapy, may be deleterious, resulting in increased myocardial oxygen consumption and reduction in diastolic filling. Considering that IVA has not negative inotropic action, it may present a potential mean to handle tachycardia in cardiogenic shock. In a recent study, patients with cardiogenic shock, who were unable to tolerate beta-blockers, started on IVA[55]. Each patient had a cardiac magnetic resonance imaging, echocardiogram, and coronary angiogram for determination of aetiology. Invasive haemodynamics via pulmonary artery catheterization were measured with continuous telemetry monitoring for any dysrhythmia or bradyarrhythmias. All patients tolerated IVA initiation, and a decrease in HR (91.6 ± 6.4 b.p.m. versus 106 ± 6.8), pulmonary arterial occlusion pressure (24 ± 5.1 mmHg versus 30.4 ± 4.8), and right atrial pressure (9 ± 4.3 mmHg versus 16.8 ± 6.2) were observed. An improvement was registered also in mixed venous oxygen saturation (64.8 ± 5.3 % versus 51 ± 8.8 %), stroke volume and right and left ventricular stroke work index[55].

IVA also appeared to be an effective alternative to Amiodarone[56,57] in children with post-operative junctional ectopic tachycardia (JET). JET is the commonest tachyarrhythmia in the early post-operative period in children undergoing open-heart surgery. It frequently leads to hemodynamic instability and needs to be managed aggressively. Amiodarone is the first-line agent along with non-pharmacological interventions but in a very recent study, all patients responded to Ivabradine. The initial response was rate control permitting overdrive pacing with only one patient having recurrence of JET 10 h after IVA administration.

CONCLUSIONS

IVA avoids the negative inotrope effects, and in patients with HFrEF, it improves the outcome and might be a first choice of therapy when HR is above 70 bpm. In addition, the fact that it is possible to treat patients who do not respond to the usual therapy clearly accentuates the importance of this new treatment option. Although some doubt still exists about the effects of IVA on mortality and morbidity outcome in HF patients, it is well recognized that IVA positively improves quality-of-life measurements and symptoms, as proven in the SHIFT and BEAUTIFUL studies among others. In addition, a reversion of left ventricular remodelling was found.

IVA has anti-ischemic and antianginal efficacy equivalent to that of β-blockers and CCBs in CSA, with effects on myocardial ischemia even greater than those predicted by HR reduction with β-blockers, suggesting favorable benefits of HR reduction with IVA versus other HR-reducing therapies. These include preservation of myocardial contractility, ventricular relaxation, prolongation of diastolic perfusion time and therefore myocardial perfusion, preservation of physiological mechanisms allowing hemodynamic adaptation to exercise, and coronary vasodilatation. In addition, IVA appears to be an effective alternative to Amiodarone in children with post-operative JET based on an early clinical experience.

IVA therapy has a lower risk of bradycardia, which is one of the main problems with other HR-lowering drugs. Bradycardia is mentioned as a side effect, although not as prevalent as reported for other drugs. This is, however, a cause of concern and should be investigated in future studies. Furthermore, ivabradine has shown promising results in the treatment of various other conditions related to cardiac impairment and electrical conduction abnormalities[60].

Cardiovascular disease remains the leading cause of death globally[61], because of an increasing prevalence of cardiovascular risk factors such as physical inactivity, obesity and diabetes mellitus. In order to reduce cardiovascular morbidity and mortality, the most appropriate pharmacological approach together with life-style change and nutritional cardiovascular prevention could be the new frontier: dietary introduction of antioxidant molecules and polyunsatured fatty acids, may substantially reduce markers of oxidative stress, thus contributing to partly prevent cardiovascular diseases by inhibiting the inflammatory responses, improving platelet function, blood pressure and fluidity with a range of protective cardiovascular effects[62-68]. The availability of these supports to the physician will increase the options in the medical management of patients with CVD.

REFERENCES

1. Perret-Guillaume C, Joly L, Benetos A. Heart rate as a risk factor for cardiovascular disease. Prog Cardiovasc Dis. 2009;52(1):6-10.
2. Hjalmarson A, Gilpin EA, Kjekshus J, Schieman G, Nicod P, Henning H, et al. Influence of heart rate on mortality after acute myocardial infarction. Am J Cardiol. 1990;65(9):547-53.
3. Thorup L, Simonsen U, Grimm D, Hedegaard ER. Ivabradine: Current and future treatment of heart failure. Basic Clin Pharmacol Toxicol. 2017;121(2):89-97.
4. Fox K1, Borer JS, Camm AJ, Danchin N, Ferrari R, Lopez Sendon JL, et al. Resting heart rate in cardiovascular disease. J Am Coll Cardiol. 2007;50(9):823-30.
5. Gammone MA, Vicentini A, Riccioni G, DeGirolamo M, D'Aulerio A, D'Orazio N. Case report food-related atrial fibrillation? The potential role of biogenic amines in "nutri-arrhythmias" genesis. Reports. 2019;2:1-11.
6. Braunwald E. Heart Failure. JACC Heart Fail. 2013;1(1):1-20.
7. Muller-Werdan U, Stockl G, Werdan K. Advances in the management of heart failure: the role of ivabradine. Vasc Health Risk Manag. 2016;12:453-470.
8. Borer JS, Tavazzi L. Update on ivabradine for heart failure. Trends Cardiovasc Med. 2016;26(5):444-9.
9. Nawarskas JJ1, Bowman BN, Anderson JR Ivabradine: A unique and intriguing medication for treating cardiovascular disease. Cardiol Rev. 2015;23(4):201-11.
10. Bortone AS, Hess OM, Gaglione A, Suter T, Nonogi H, Grimm J, et al. Effect of propranolol on coronary vasomotion in response to sympathetic stimulation in humans: importance of the functional integrity of the endothelium. Circulation. 1990;81:1225–35.
11. Tattersfield AE. Respiratory function in the elderly and the effects of betablockade. Cardiovasc Drugs Ther. 1991; 4:1229–32.
12. DiFrancesco D. Cardiac pacemaker If, current and its inhibition by heart rate reducing agents. Curr Med Res Opin. 2005;21:1115-1122.
13. Gammone MA, Riccioni G, Massari F, D'Orazio N. Beneficial Effect of Ivabradine against cardiovascular diseases. Front in Bioscience. 2020.

14. Alshammari TM. Ivabradine, do the benefits outweigh the risks? J Cardiovasc Pharmacol Ther. 2016;2:170-177.
15. Romanelli MN, Sartiani L, Masi A. HCN channels modulators: The need for selectivity. Curr Top Med Chem. 2016;16(16):1764-91.
16. Koruth JS, Lala A, Pinney S, Reddy VY, Dukkipati SR. The Clinical Use of Ivabradine. J Am Coll Cardiol. 2017;70(14):1777-1784..
17. Riccioni G. Ivabradine: from molecular basis to clinical effectiveness. Adv Ther. 2010;27:160-7.
18. Baruscotti M, Barbuti A, Bucchi A. The cardiac pacemaker current. J Mol Cell Cardiol. 2010;48:55-64.
19. DiFrancesco D. The role of the funny current in pacemaker activity. Circ Res. 2010;106:434-46.
20. Borer JS, Tardif JC. Efficacy of ivabradine, a selective I(f) inhibitor, in patients with chronic stable angina pectoris and diabetes mellitus. Am J Cardiol. 2010;105:29-35.
21. Manz M, Reuter M, Lauck G, Omran H, Jung W. A single dose of ivabradine, a novel If inhibitor, lowers heart rate but does not depress left ventricular function in patients with left ventricular dysfunction. Cardiology. 2013;100:149-55.
22. DeFerrari GM, Mazzuero A, Agnesina L, Bertoletti A, Lettino M, Campana C, et al. Favourable effects of heart rate reduction with intravenous administration of ivabradine in patients with advanced heart failure. Eur J Heart Fail. 2008;10:550-5.
23. Riccioni G. Focus on ivabradine: a new heart rate-controlling drug. Expert Rev Cardiovasc Ther. 2009;7:107-13.
24. Fox K, Ford I, Steg PG, Tendera M, Ferrari R, BEAUTIFUL Investigators. Ivabradine for patients with stable coronary artery disease and left-ventricular dysfunction (BEAUTIFUL), a randomized, double-blind, placebo-controlled trial. Lancet. 2008;372:807-16.
25. Savelieva I, Camm AJ. Novel If current inhibitor ivabradine, safety considerations. Adv Cardiol. 2006;43:79-96.
26. Murat SN, Orcan S, Akdemir R, Dogan M, Kara E, Balci M. Arrhythmic effects of ivabradine in patients with coronary artery disease. Clin Invest Med. 2009;32:322-6.
27. Tardif JC. Ivabradine, I(f) inhibition in the management of stable angina pectoris and other cardiovascular diseases. Drugs Today. 2008;44:171-81.
28. Baka T, Simko F. Ivabradine modulates the autonomic nervous system by affecting the "little brain" of the heart: A hypothesis. Med Hypotheses. 2019;129:109253.
29. Tardif JC, Ford I, Tendera M, Fox K, INITIATIVE Investigators. Efficacy of ivabradine, a new selective If inhibitor, compared with atenolol in patients with chronic stable angina. Eur Heart J. 2005;26:2529-36.
30. DeSilva R, Fox KM. Angina, Ivabradine for treatment of stable angina pectoris. Nat Rev Cardiol. 2019; 6:329-30.
31. Ripa C, Germano G, Caparra A, Capparuccia CA, Antonicelli R. Ivabradine use in refractory unstable angina, a case report. Int J Immunopathol Pharmacol. 2009;22(3):849-52.
32. Köster R, Kaehler J, Meinertz T; REDUCTION Study Group. Treatment of stable angina pectoris by ivabradine in every day practice: the REDUCTION study. Am Heart J. 2009;158(4):e51-7.
33. Tendera M, Borer JS, Tardif JC. Efficacy of I(f) inhibition with ivabradine in different subpopulations with stable angina pectoris. Cardiology. 2009;114(2):116-25.
34. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R, et al. Heart rate as a prognostic risk factors in patients with coronary artery disease and left-ventricular dysfunction (BEAUTIFUL), a subgroup analysis of a randomised controlled trial. Lancet. 2008;372:817-21.
35. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R. Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized, controlled BEAUTIFUL trial. Eur Heart J. 2009;30: 2337-45.
36. Swedberg K1, Komajda M, Böhm M, Borer JS, Ford I, Tavazzi L. Rationale and design of a randomized, double-blind, placebo-controlled outcome trial of ivabradine in chronic heart failure: the Systolic Heart Failure Treatment with the I(f) Inhibitor Ivabradine Trial (SHIFT). Eur J Heart Fail. 2010;12(1):75-81.
37. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT), a randomised placebo-controlled study. Lancet 2010;376(9744):875-85.
38. Calò L, Rebecchi M, Sette A, Martino A, de Ruvo E, Sciarra L, et al. Efficacy of ivabradine administration in patients affected by inappropriate sinus tachycardia. Heart Rhythm. 2010;7(9):1318-23.
39. Sette A, Martino A, Lioy E, Calò L. Efficacy of ivabradine in a case of inappropriate sinus tachycardia and ventricular dysfunction. J Cardiovasc Electrophysiol. 2010;21(7):815-7.
40. DeSisti A, Tonet J, Benkaci A, Frank R. A case of inappropriate sinus tachycardia after atrio-ventricular nodal reentrant tachycardia cryoablation successfully treated by ivabradine. Europace. 2010;12:1029-31.
41. Capulzini L, Sarkozy A, Semeraro O, Paparella G, Chierchia GB, DE Asmundis C, et al. Ivabradine to treat inappropriate sinus tachycardia after the fast pathway ablation in a patient with severe pectus excavatum. Pacing Clin Electrophysiol. 2010;33(3):e32-5.
42. Kaplinsky E, Comes FP, Urondo LS, Ayma FP. Efficacy of ivabradine in four patients with inappropriate sinus tachycardia: a three month-long experience based on electrocardiographic, Holter monitoring, exercise tolerance and quality of life assessments. Cardiol J. 2010;17(2):166-71.
43. Kumar S, Vohra J. Ivabradine, Appropriate treatment for inappropriate sinus tachycardia. Heart Rhythm. 2010;7:1324-5.
44. Kaczmarek K, Klingenheben T, Poddebska I, Urbanek I, Wranicz JK, Cygankiewicz I. Baseline intrinsic heart rate and response to ivabradine treatment in patients with inappropriate sinus tachycardia. Ann Noninvasive Electrocardiol. 2019:e12709.
45. Zhang R, Haverich A, Strüber M, Simon A, Pichlmaier M, Bara C. Effects of ivabradine on allograft function and exercise performance in heart transplant recipients with permanent sinus tachycardia. Clin Res Cardiol. 2008;97(11):811-9.
46. Doesch AO, Ammon K, Konstandin M, Celik S, Kristen A, Frankenstein L, et al. Heart rate reduction for 12 months with ivabradine reduces left ventricular mass in cardiac allograft recipients. Transplantation 2009;88(6):835-41.
47. Zwicker C, Becker M, Lepper W, Koch KC, Westenfeld R. Cardiogenic Shock due to tachycardiomyopathy after Heart Transplantation: Successful Treatment with Ivabradine. Cardiology. 2010;116(3):174-7.
48. Zhang R, Bobylev D, Stiefel P. Lasting reduction of heart transplant tachycardia with ivabradine is effective and well tolerated: results of 48-month study. Clin Res Cardiol. 2012;101(8):631-6.
49. Gammone MA, Riccioni G, Parrinello G, D'Orazio N. Omega-3 Polyunsaturated Fatty Acids: Benefits and Endpoints in Sport. 2018;11(1): E46.
50. Riccioni G, Gammone MA, Currenti W, D'Orazio N. Effectiveness and Safety of Dietetic Supplementation of a New Nutraceutical on Lipid Profile and Serum Inflammation Biomarkers in Hypercholesterolemic Patients. Molecules 2018;14:23(5):E1168
51. Bonadei I, Sciatti E, Vizzardi E, Fabbricatore D, Pagnoni M, Rossi L, et al. Effects of ivabradine on endothelial function, aortic properties and ventricular-arterial coupling in chronic systolic heart failure patients. Cardiovasc Ther. 2018;36(3):e12323
52. Custodis F, Baumhäkel M, Schlimmer N, List F, Gensch C, Böhm M, et al. Heart rate reduction by ivabradine reduces oxidative stress, improves endothelial function, and prevents atherosclerosis in apolipoprotein E-deficient mice. Circulation 2008;117(18):2377-87.
53. Triggle CR. Defying the economists: a decrease in heart rate improves not only cardiac but also endothelial function. Br J Pharmacol. 2008;154:727-8.
54. Drouin A, Gendron ME, Thorin E, Gillis MA, Mahlberg-Gaudin F, Tardif JC. Chronic heart rate reduction by ivabradine prevents endothelial dysfunction in dyslipidaemic mice. Br J Pharmacol. 2008;154(4):749-57.
55. Chiu MH, Howlett JG, Sharma NC. Initiation of ivabradine in cardiogenic shock. ESC Heart Fail. 2019;6(5):1088–1091.
56. Krishna MR, Kunde MF, Kumar RK, Balaji S. Ivabradine in Post-operative Junctional Ectopic Tachycardia (JET): Breaking New Ground. Pediatr Cardiol. 2019;40(6):1284-1288.
57. Dieks JK, Klehs S, Müller MJ, Paul T, Krause U. Adjunctive ivabradine in combination with amiodarone: A novel therapy for pediatric congenital junctional ectopic tachycardia. Heart Rhythm. 2016;13(6):1297-302.
58. Moubarak G, Logeart D, Cazeau S, Solal AC. Might ivabradine be useful in permanent atrial fibrillation? Int J Cardiol. 2014;175(1):187-8.
59. Kosiuk J, Oebel S, John S, Hilbert S, Hindricks G, Bollmann A. Ivabradine for rate control in atrial fibrillation. Int J Cardiol. 2015;179:27-8.

60. Rosano GM, Vitale C, Volterrani M. Heart rate in ischemic heart disease. The innovation of ivabradine: more than pure heart rate reduction. Adv Ther. 2010;27:202-10.

61. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006;3:e442.

62. Gammone MA, Riccioni G, D'Orazio N. Carotenoids, Potential allies of cardiovascular health? Food Nutr Res. 2015;59:26762.

63. Gammone MA, Riccioni G, D'Orazio N. Marine carotenoids against oxidative stress: Effects on human health. Mar Drugs. 2015;13:6226–6246.

64. Gammone MA, Tettamanti G, Bergante S, Pulchinotta FR, D'Orazio N. Prevention of cardiovascular diseases with carotenoids. Front Biosci. (Schol Ed.) 2017;9:165–171.

65. Gammone MA, Efthymakis K, Pluchinotta FR, Tettamanti G, Bergante S, Riccioni G, et al. Impact of chocolate on the cardiovascular health. Front Biosci. (Landmark Ed.) 2018;23:852–864.

66. Gammone MA. Carotenoids, ROS, and cardiovascular health (Book Chapter). Reactive Oxygen Species in Biology and Human Health. CRC Press. 2017.

67. Riccioni G, Gammone MA, Tettamanti G, Bergante S, Pluchinotta FR, D'Orazio N. Resveratrol and anti-atherogenic effects. Int J Food Sci Nutr. 2015;66(6):603-10.

68. D'Orazio N, Gammone MA, Gemello E, De Girolamo M, Cusenza S, Riccioni G. Marine bioactives: pharmacological properties and potential applications against inflammatory diseases. Mar Drugs. 2012;10(4):812-33.

Cite this article : Gammone MA. Review Article: Impact of Ivabradine on Cardiovascular Morbidity. J Cardiovascular Disease Res. 2020; 11(1): 04-08.